FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING

DAY ONE

Rockville, Maryland

Wednesday, January 7, 2009

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PUBLIC COMMENT:

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SCOTT CROSSLAND

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PATRICIA GIBSON

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STEVEN SCHACHTER

MARK VEASEY

ANNA WOLLOCK

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P R O C E E D I N G S

(8:00 a.m.)

DR. GOLDSTEIN: Good morning. I hope everybody had a safe trip here through the inclement weather today. My name is Larry Goldstein. I'm the acting chair for the meeting today. I want to welcome everybody. Before we go around the table and introduce the committee members, I have a couple of statements I need to go through.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair -- that means me. We look forward to a

productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of the meeting with the media until its conclusion. A press conference will be held in the Washington Room immediately following the meeting today. Also, the Committee is reminded to please refrain from discussing the meeting topic during lunch breaks, dinner breaks, or any other breaks.

Thank you all for trying to follow those guidelines.

I'd like to begin next by having the members of the Committee introduce

themselves. This is an incredibly large group. I think I need binoculars to see the people down at that end. You'll have to shoot up flares or something to get my attention later. But why don't we start down there and then go around. That'll take us a good 10 minutes, I think.

DR. TWYMAN: Good morning. My name is Roy Twyman. I'm the industry rep.

MR. BARTENHAGEN: Mike Bartenhagen, and I'm the patient rep.

DR. MIZRAHI: I'm Eli Mizrahi. I'm the chair of the Department of Neurology at Baylor College of Medicine. I'm a child neurologist. I have interest in epilepsy.

DR. WEINSTEIN: I'm Steve Weinstein. I am director of the pediatric epilepsy program at Weill Cornell Medical School at New York Hospital.

DR. JENSEN: I'm Frances Jensen. I'm director of the epilepsy research program at Children's Hospital Boston, and also on staff at

the Brigham Women's Hospital, in neurology.

DR. CHUGANI: I'm Harry Chugani. I'm a pediatric neurologist, head of child neurology at Children's Hospital Michigan, Wayne State University.

DR. DURE: I'm Leon Dure. I'm the chief of child neurology at the University of Alabama-Birmingham, and a representative of the Pediatric Advisory Committee.

DR. SNODGRASS: I'm Wayne Snodgrass, and a pediatrician and clinical pharmacologist and medical toxicologist at the University of Texas Medical Branch.

DR. GORMAN: I'm Rich Gorman, a pediatrician with 25 years of private practice experience, and a clinical associate professor at the University of Maryland.

DR. HECKERT: I'm Richard Heckert. I'm a pediatric ophthalmologist in private practice in Green Bay, Wisconsin.

DR. WEST: I'm Constance West. I'm a pediatric ophthalmologist and head of pediatric

ophthalmology at Cincinnati Children's Hospital.

DR. ROGAWSKI: My name is Michael Rogawski. I'm a neurologist and neuropharmacologist. I'm professor and chairman of neurology at the University of California at Davis.

DR. VEGA: Good morning. My name is Mary Alice Vega. I am a staff research nurse with the New Jersey Medical School in Newark, New Jersey. I'm a former member of the Risk Communication Advisory Committee.

DR. SLEATH: Hi, I'm Betsy Sleath, professor of Pharmaceutical Outcomes and Policy at the University of North Carolina-Chapel Hill, and current member of the FDA's Risk Communication Committee.

DR. NGO: My name is Diem-Kieu Ngo, the federal official for this meeting. The designated federal official.

DR. JUNG: I'm Lily Jung. I'm the consumer rep, and I am a neurologist at Swedish Neuroscience Institute in Seattle, and a

clinical associate professor of neurology at the University of Washington.

DR. RIZZO: I'm Matt Rizzo. I'm a member of the PNSCNS committee. I'm professor of neurology at Iowa, and I'm the vice chair for translational and clinical research.

DR. BALISH: I'm Marshall Balish. I'm the assistant chief of neurology at the Veterans Hospital. I'm a neurologist and epileptologist and associate clinical professor at Georgetown.

DR. LU: I'm Ying Lu, professor at the University of California-San Francisco. I'm a statistician, and also member of PCNS committee.

(Sound Interruption)

SPEAKER: It's not just you.

SPEAKER: We're troubleshooting.

DR. van BELLE: Gerald van Belle, Department of Biostatistics at University of Washington, Seattle.

DR. CRAWFORD: Good morning. I'm Stephanie Crawford, associate professor and associate head department of pharmacy

administration at the University of Illinois-Chicago, and a former member of the Drug Safety and Risk Management Advisory Committee.

DR. KRAMER: Hi, I'm Judith Kramer. I'm associate professor of medicine at Duke University, in general internal medicine. And I have a background in clinical -- about 20 years in clinical research -- both clinical trials and observational studies of effectiveness and safety. I'm on the Drug Safety and Risk Management Advisory Committee.

DR. GARDNER: Good morning. I'm Jacqueline Gardner, University of Washington School of Pharmacy. And I'm a former member of the Drug Safety and Risk Management Advisory Committee.

DR. LESAR: Timothy Lesar, director of clinical pharmacy services at Albany Medical Center in Albany, New York. And I'm a member of the Drug Safety and Risk Management Committee.

DR. NELSON: Louis Nelson. I'm an

associate professor of emergency medicine and a medical toxicologist at NYU.

DR. FARKAS: Ronald Farkas, from the Division of Neurology Products at FDA.

DR. HERSHKOWITZ: Norm Hershkowitz, from the Division of Neurology Products. I'm a medical team leader.

DR. CHAMBERS: Wiley Chambers, Division of Anti-Infective Ophthalmology Drugs.

DR. KATZ: Russ Katz. I'm the director of the Division of Neurology Products FDA.

DR. GOLDSTEIN: And Dr. Hirtz, you just came in.

DR. HIRTZ: Deborah Hirtz. I'm a child neurologist and programs director at NINDS.

DR. GOLDSTEIN: Thank you.

Dr. Ngo is now going to read the conflict of interest statement.

DR. NGO: Good morning. Before I do that, I just want to remind everyone to silence

your cell phones and pagers if you haven't already done so. And also, if the press officer is here, Ms. Sandy Walsh -- if you're here, please stand up. Okay. She should be here throughout the day.

The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting and non-voting members of the Committee are special government employees, or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC Section 208 and Section 712 of the

Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting and non-voting members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal --

(Sound Interruption)

DR. NGO: Let me just start from that paragraph again.

FDA has determined that members and temporary voting and non-voting members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts of interest, when it is determined that the

Agency's need for a particular individual service outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal government employees with potential financial conflicts, when necessary, to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting and non-voting members of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and

royalties, and primary employment. Today's agenda involves new drug application (NDA) 20-427, vigabatrin, sponsored by Ovation Pharmaceuticals, Inc., for the proposed indication of adjunctive therapy for the treatment of refractory complex partial seizures in adults.

This is a particular matters meeting during which specific matters related to vigabatrin will be discussed. With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Twyman is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry.

Dr. Twyman's role at this meeting is to represent industry in general and not any particular company. Dr. Twyman is employed by Johnson & Johnson.

We would like to remind members and temporary voting members that if the

discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and the exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. GOLDSTEIN: Thank you. For the members of the Committee, I'll also just remind you before we get started further that there is a thing there for lunch for you to fill out. Fill it out now. Believe it or not, getting lunch at these things is probably one of the more difficult things that we have to try to work out.

The meeting today -- the problem is quite complex. And for those of you who have been on these committees before, you know

that we have a limited -- we usually have a limited number of questions and a limited number of things that we need to discuss for the FDA.

If you looked at the questions, and I hope everyone has, the list is extensive. And each one of the questions has sub-questions. If you just do the math, we have about an hour and 45 minutes to 2 hours this afternoon to discuss each one of these questions and sub-questions. So if you divide, that's about 10 minutes or less for each major question, and 30 seconds or less for some of these sub-questions.

So it's going to be a challenge to try to do what we need to do. So for all of the Committee members and all of the presenters, we need to try to keep things succinct, and to the point, and focused, and on target. So for all the presentations that are going to be coming up, I'm going to ask each of the presenters to try to really stay

on -- right on time.

We have a section after the presentations for the Committee to ask specific clarifying questions. Sometimes we tend to go on in different directions. I'm really going to try to keep us focused today, just because of the complexity of the issues and the number of things that we need to get through.

So having said that, next are the introductory remarks from Dr. Katz.

DR. KATZ: Is this -- okay, thanks, Dr. Goldstein. I'll try to take your comments about being brief to heart. I just have really a very few brief introductory remarks.

First, I'd like to welcome the Committee as well. And in particular, I'd like to welcome all the invited experts who have agreed to come and help us over the next two days in what I hope you will agree will be a very interesting and, as Dr. Goldstein has already remarked, challenging task.

As you know, we're here to discuss two applications over the next two days related to Sabril, a GABA-transaminase inhibitor being proposed as an anticonvulsant in two different NDAs submitted by Ovation Pharmaceuticals for two distinct indications -- adjunctive treatment for partial seizures in adults, which we will be talking about today. That's NDA-20427. And there's a treatment for infantile spasms. That's under NDA-22006.

As you undoubtedly know and as Dr. Goldstein has already pointed out, the drug has had a very long, very complex regulatory history. And I will be, I hope, extremely brief in these remarks. I just want to outline that history and some of the major points along the way as the drug was being developed, and outline some of the major issues that we would like you to discuss over the next couple of days.

Briefly, the IND for this drug was

submitted in 1980. Shortly thereafter in 1983, a unique histopathologic lesion was noted in at least three animal species tested, more or less at the doses that humans would be receiving. And because of this lesion, which was characterized by vacuoles between myelin lamellae and in numerous brain regions, and subsequently referred to as intramyelinic edema or IME, clinical studies were halted until the sponsor was able to identify and validate a non-invasive method for detecting the lesion in animals at a stage early enough so that if it could -- we could prevent any progression of the lesion if the drug were discontinued.

So after several years, the sponsor was able to validate several surveillance methodologies, including potentials in MRI as being relatively sensitive in various species to the onset of the lesion. And so studies in humans were permitted to resume. And at that time, the sponsor was developing the

drug to treat partial seizures in adults.

And I should point out that all of the work -- all of the clinical trials in both indications that we're going to be discussing over the next couple of days were performed under the auspices of either another commercial sponsor or academic investigators. Ovation Pharmaceuticals took over the product relatively recently, and has submitted the NDAs in front of us today. All the work was done by others.

So NDA-20427 was submitted, again, by another sponsor in April 1994, contained the results of two controlled trials in adults with partial seizures. And we issued a not approvable letter in response to that initial submission, but we had provisionally determined that the sponsor had in fact submitted substantial evidence of effectiveness for the drug as adjunctive treatment for partial seizures.

And just briefly for those who

aren't familiar with the process, substantial evidence of effectiveness is the legal requirement for a demonstration of effectiveness for a drug ordinarily defined as basically -- at least to so-called adequate and well-controlled trials -- that demonstrate the effect that the sponsor proposes it has.

And then subsequently, in an approval letter dated November 1997, we agreed that effectiveness in that population had been demonstrated -- that is as adjunctive treatment in adults with partial seizures. But we said that it should be indicated as second-line treatment because of the unknown clinical consequences of the intramyelinic edema.

But by the time the sponsor responded to that approvable letter, and they responded in April 1998, we had become aware of a unique visual field defect associated with Sabril treatment. And although the

sponsor at that time proposed that the drug be approved as a last resort treatment for patients who had failed in everything else, under fairly restrictive conditions, we concluded that the risk of the visual field defect had not been adequately characterized. And we issued another not approvable letter.

And then after numerous discussions with the current sponsor, who took over the project relatively recently, as I said, they have submitted a response to that not approvable letter that we issued many years ago. And it's that response and subsequent submissions that serve as the basis for today's meeting.

Today, we really do expect to spend most of the day considering the nature of the visual field defect caused by Sabril. As I noted earlier, we had already concluded that there was substantial evidence of effectiveness for Sabril as adjunctive treatment for complex partial seizures in

adults, and we're not specifically asking you for your views on that data, specifically. However, of course, any decision about whether or not this application should be approved rests on a consideration of the risks and the benefits. So in that regard, you will need to know something about those results. They are described in your book, and I think you'll hear them from the company, at least briefly. And you'll need to take that into consideration when you make your decisions.

Just briefly, after my remarks this morning, the sponsor will make their formal presentation about the safety and effectiveness data. We will only make -- we, the Agency, will only make two formal presentations. One by Dr. Ron Farkas of the Division, who will give the Agency's views of the ophthalmic findings in adults, and Dr. Joyce Weaver from the Agency's Office of Surveillance and Epidemiology.

And she'll give the Agency's views about the sponsor's proposed risk evaluation and mitigation strategy, or REMS, as it's called, which is basically a plan to attempt to minimize the potential for risk should the drug be approved.

So I'm not going to be spending any time at all this morning talking about any of the data. I do want to highlight some of the main issues that we'd like you to consider over the next couple of days. Ultimately, we're interested to know if you believe that there are any conditions under which Sabril could be approved for use as adjunctive treatment for partial seizures in adults.

If you do think that there are conditions that would justify approval, we need to know more or less specifically what combination of patient population and conditions of use would support approval.

For example, as I said, we believe that the controlled trials already to date in

adults demonstrate substantial evidence of effectiveness, but we also believe those trials enroll the sorts of patients that are typically enrolled in drug trials of new anti-convulsants.

Namely, these are patients who failed to respond adequately to one, or two, or maybe three previously tried anti-convulsants, although the Sabril data, of course, being relatively old, those patients have not been shown to be inadequately treated on any of the newer anti-convulsants. They were mostly treated with old standby treatments, which, of course, are still available.

So for example, we'd like to know if you believe, given what you'll hear about as far as the risks, that that's sufficient evidence of effectiveness to justify approval, or whether or not patients should be -- whether or not the sponsor should do trials in patients who are even more

refractory and meet with a more stringent definition of refractory. Maybe failed on two, three, four, five drugs. Maybe some of the newer drugs. Or whether or not the sponsor should do studies in which patients who fail on treatment are re-randomized to some treatment or Sabril in an attempt to show some true superiority.

These are the sorts of questions that I think we're going to want you to discuss with regard to the question of effectiveness. Critically, of course, we need to know your views about the nature of the visual field defect induced by Sabril, and in particular whether or not you think that is sufficiently characterized to support approval at this time.

For example, do we know enough about the lesion that if it occurs, it progresses with continued treatment? Does it not progress with continued treatment? Is it reversible upon drug discontinuation? Does

it progress if the drug is discontinued? These are all the sorts of issues that we need to have you discuss today.

In addition, do you think we know enough about the time course of the visual field defect? Do the data suggest that it occurs slowly and progressively? Or does it occur abruptly? And it can occur abruptly even after long-term treatment or after brief treatment. These are all the sorts of difficult questions that we're faced with that we need you to talk about.

And of course, all of these questions are related to the all-important question of whether or not the sponsor's identified a method of monitoring for the lesion that's sufficiently sensitive to pick it up at a clinically meaningless or early state. And by that I mean whether or not there are specific tests or a specific test that can pick it up sufficiently early, and/or whether or not there's a monitoring

paradigm in terms of, let's say for example, frequency of monitoring that can reliably identify the lesion early.

And Dr. Farkas, as I said before, will present our views about whether or not the natural history of the lesion has been adequately characterized, as well as our views of the sponsor's claims that they have in fact identified a sensitive method and surveillance regime to monitor for the visual lesion.

Certainly, if you do believe that there are conditions under which the application can ultimately be approved, we need to know whether or not you think it should be made available under certain restricted conditions. And if so, we need to know your views on what those restricted conditions might be.

Finally -- and that, of course, has to do with the REMS. And finally, we need to ask you specifically whether or not you

believe that the application should be approved with the data we have in hand. You may feel that given the uncertainties related, for example, to the visual field defect, that yes, even so, this should be approved with the data in hand. That's critical, of course, because that's the application in front of us. And so we have to ask you that question.

Tomorrow, we'll be discussing NDA-22006 for the use of Sabril in the treatment of infantile spasms. I just want to briefly -- a couple of housekeeping notices about tomorrow. You have a revised agenda in your book. I think originally we were going to start at 8:00 tomorrow as we have been today, but in an attempt to increase the amount of time available for discussion tomorrow, we're going to start at 7:30 instead of 8:00. And I think we are scheduled to adjourn at -- sorry, scheduled to adjourn at 5:30.

And for the same reason, I won't be making any opening remarks. We'll save a few minutes there tomorrow, and Dr. Julia Long, who is the Agency's statistician who is listed in the agenda -- the original agenda anyway -- as making a separate presentation will not. And Dr. Phil Sheridan from the Division will be making more or less the combined clinical and statistical presentation for the Agency. So we hope to save a little bit of time in the formal agenda tomorrow to have some more time for discussion.

In tomorrow's application, we will explicitly ask you whether or not you think the sponsor has submitted substantial evidence of effectiveness for Sabril as a treatment for infantile spasms, because we have not encountered that question before. This is the first application that contains that data.

So I would note, though -- and

Dr. Sheridan will go into some more detail about this and I'm sure the company will as well tomorrow -- the studies that are submitted in support of that claim do vary quite considerably from the usual sorts of data that we get in applications in terms of prospective conduct of the trial, analysis of the trial, even the design of the trial -- there will be many elements in those areas that you'll see that sort of vary considerably from the sorts of trials that commercial sponsors typically do to get a drug approved. Those trials for infantile spasms were done by academic investigators. So there will be a number of issues related to that when we deal about effectiveness tomorrow.

And of course, with regard to the risk of visual field defect in those -- in that pediatric population, as well as overall risk-benefit considerations, we're going to have many of the same questions for that

population that we will today, and that I've outlined and as Dr. Goldstein has already suggested or detailed in your book now. So I'm not going to go over those.

Just to say that -- the question about whether or not there are reliable methods to pick up this lesion in the pediatric population takes on a particular urgency, because those patients are not capable of reporting any symptoms that might be referable to a visual field defect. So that's a whole other layer of difficulties in that population.

And again, tomorrow, Dr. Farkas will present the Agency's views of the ophthalmic data in children and our view of whether or not we think the sponsor has in fact identified a sensitive method to pick those lesions up.

So -- and in addition to the visual toxicity in pediatric patients, recently an unusual MRI finding has been detected, and as

a result of that, we asked the sponsor to go back and look at all their MRI data in adults as well, which were originally claimed to be negative. But this lesion occurs in a location that wouldn't have been predicted if we thought it was representative of intramyelinic edema. And Dr. Sheridan tomorrow will present our view of what we think about those findings of the re-review of the MRI.

The sponsor suggests that this might be intramyelinic edema just in a different location. Tomorrow, we're going to hear a presentation from Dr. Larry Schmued, who is a toxicologist in the Agency's National Center for Toxicological Research.

And he's going to present his review of histopathologic lesions found in juvenile animals. To the extent that that could be potentially related to the MRI lesion, we'll hear about that.

Unfortunately, Dr. Schmued cannot

be here in person tomorrow. We will show his slides and he will present by phone so we'll be able to hear him and he'll be available for questions. But unfortunately, he can't be here in person. But I would like to thank him very much for making the effort to do that.

And then of course, ultimately tomorrow, as today, we'll need to ask you whether or not you think the application for infantile spasms can be approved with the data in hand, because again, that's the data that we have, and that's the application we have to act on.

So just a couple of quick questions about the question -- statements about the question list that Dr. Goldstein mentioned. As you've heard and as you've seen, there are many questions. There are many sub-questions. They're very complicated. They're very complex. And I apologize for the complexity. It is unusual for us. But

they were designed to ensure that we get your input on all the questions that we think are relevant for consideration of these issues.

I think almost after every one, it says yes, no, abstain -- the implication being that we will take a formal vote on all of those questions. I don't think we need to take a formal vote on all of those questions. We'll have to decide as the discussion progresses which ones we think we need to actually get a formal vote on, and which ones we think we just need to get a sense of the Committee about. So I think there's room for flexibility.

As always, if there are issues that you want to discuss that are relevant that we have not captured in the questions, which is hard to imagine, looking at that question list, but it's certainly possible -- so if you do, we certainly want you to raise, those because we certainly want you to consider everything that you think important to tackle

this task.

So with that, I'll hand the meeting back to Dr. Goldstein. Again, thanks for coming. Thanks for all the work you've done in preparation, and thanks for the work you're about to do.

Thanks.

DR. GOLDSTEIN: So just for the Committee again, just to highlight exactly the framework and the things to keep in mind, the questions that we need to be addressing is are there any conditions that would justify the approval of this drug? Is there a need for additional effectiveness data? Has the natural history of the visual field defect been adequately -- has it been adequately characterized?

Has the sponsor identified a reliable sensitive monitoring scheme? And can the NDA be approved with the data in hand? So that's sort of just the focus just to keep in mind.

With that, let's go on now to the industry presentations. The first is from Dr. Cunniff.

DR. CUNNIFF: Dr. Goldstein, Dr. Temple, Dr. Katz, Dr. Chambers, members of the advisory committees, members of the FDA review team, ladies and gentlemen, good morning.

My name is Tim Cunniff, and I head up the Regulatory Affairs Pharmacovigilance and Clinical Quality Assurance divisions for Ovation Pharmaceuticals. We are here today and tomorrow to discuss Sabril, or vigabatrin. Vigabatrin is a very effective anti-seizure drug with a serious side effect which has limited its use -- specifically, the peripheral visual field defect. Given this consideration, Ovation has focused approval efforts on two devastating forms of epilepsy.

Today, we're going to discuss the first indication, which is shown here. Sabril for the adjunctive therapy of

refractory complex partial seizures in adult patients. Our definition of refractory is intended to convey that the drug should be reserved for those individuals who have inadequately responded to other therapies. Tomorrow, we'll discuss the indication for infantile spasms.

Although unapproved in the U.S., Sabril is widely available in most major countries throughout the world, including Canada and Mexico, where Ovation distributes the drug; most countries within the European Union and other countries in Asia, Latin America, Africa, and the Middle East. We estimate that more than 1.5 million patients have received vigabatrin since initial approval in Europe over 19 years ago.

Although Ovation's experience with Sabril only spans about 4-1/2 years, there was a 30-year development and approval history for this drug. Vigabatrin was first synthesized in 1975, and is still the only

anti-seizure drug that irreversibly inhibits GABA-T. Clinical trials began in Europe and the U.S. in 1979 and 1980, respectively. Between 1983 and 1990, new patient enrollment was suspended in the United States due to findings of intramyelinic edema in rodents and dogs during the toxicology studies.

During this time, three separate Advisory Committee meetings were convened to discuss these findings. Ultimately, the FDA agreed with the last committee recommendation to allow clinical trials in patients with uncontrolled epilepsy.

Vigabatrin's first worldwide approval came in 1989 in the United Kingdom, followed closely by many other countries in Europe. In the United States, the initial NDA was submitted by a prior sponsor in 1994, and the FDA issued an approval letter in November of 1997. However, the first reports of a PVFD emerged soon after, nearly eight years after initial marketing approval in

Europe. After consideration of that information, the FDA ultimately issued a not approvable letter in October of 1998, and requested additional information to characterize the PVFD.

In 1999, the European Medicines Agency, or EMEA, concluded that a positive benefit/risk still existed for more restrictive indications of resisting complex partial seizures and infantile spasms, the very same indications Ovation is seeking approval for in the United States. The EMEA also required post-marketing pre-clinical and clinical studies to further characterize the peripheral visual field defect. Ovation acquired the North American rights to vigabatrin in 2004, and since this time has worked to provide FDA with adequate information to assess the benefit/risk of vigabatrin therapy.

This information largely emerged from the studies that were required by the

European Medicines Agency. The last of these studies was summarized and submitted to both the EMEA and to the FDA in 2007.

In late 2006, a report of MRI abnormalities in 3 of 15 vigabatrin-treated patients with infantile spasms prompted the Agency to request additional information. Ovation gathered, summarized, and submitted this information to FDA in late 2007, and in early 2008, the FDA accepted the Sabril NDAs for review.

There are some key considerations to keep in mind throughout today's presentation. Most important, refractory complex partial seizures is a serious and life-threatening disease, and an unmet medical need still exists. The efficacy of vigabatrin for complex partial seizures is well-established, as acknowledged by FDA in their briefing document. The safety profile of vigabatrin is also well-characterized by a large number of clinical trials and

substantial post-marketing experience.

With respect to the PVFD, many essential features are now better understood since the issue was first identified 10 years ago. Estimated prevalence for PVFD is fairly high, and the risk appears to increase after prolonged exposure to the vigabatrin, and on average as reported many months after therapy is initiated. If PVFD does occur, it is usually mild to moderate in severity, appears to progress slowly, and is irreversible. Age-appropriate ophthalmologic testing can detect the PVFD, and our monitoring recommendation is meant to prevent a clinically meaningful restriction in a patient's peripheral visual field.

To further mitigate risk, Ovation will provide a comprehensive risk evaluation and mitigation strategy, or REMS, that will accompany the approval of vigabatrin, to ensure that the drug is used safely by appropriate patients. Many risk management

tools will be incorporated into the REMS, including informative labeling, many communication and educational programs, and several restrictive and enforced elements to ensure safe use, including enforced ophthalmologic monitoring in patients with complex partial seizures, and a mandatory Sabril registry.

Finally, one must consider the benefit of controlling refractory seizures in vigabatrin-responsive patients versus the risk for PVFD. The evidence we'll review today establishes a positive benefit/risk profile for vigabatrin in the treatment of adult patients with complex partial seizures who have inadequately responded to other therapies.

The rest of today's agenda is shown here. Dr. Ed Faught from the University of Alabama at Birmingham will describe the features of refractory complex partial seizures and the unmet medical need.

Dr. Chris Silber will review the efficacy and safety data. Dr. Robert Sergott from the Wills Eye Institute at Thomas Jefferson University will discuss consequences in monitoring of the peripheral field defect. Dr. Steve Sagar will present the characteristics of the PVFD. I will return to discuss our proposed REMS, and finally, Dr. Roger Porter from the University of Pennsylvania and the Uniformed Services University will conclude our presentation with a benefit/risk assessment. In addition to today's presenters, the experts listed here are available to answer any questions you may have.

I would now like to ask Dr. Faught to come up and discuss refractory complex partial seizures and the unmet medical need.

Thank you.

DR. FAUGHT: Good morning. I'm Ed Faught. I'm a professor of neurology at the University of Alabama School of Medicine, and

director of the UAB Epilepsy Center.

I'm going to discuss the problem of refractory complex partial seizures, starting with some basic information on epilepsy, and then I'll describe how refractory epilepsy affects people's lives, and then address the question of why we need additional therapies for this condition.

A seizure is a brief abnormal brain electrical discharge. The clinical features depend upon the part of the brain involved, can range from a brief loss of consciousness to a full convulsion.

Epilepsy simply means a tendency to have repeated seizures, and it's very common, affecting one to two percent of the population. There are many different causes, and the cause is unknown in about half of the patients. This host of causes suggests that there's a wide variety of biological mechanisms, and this is probably an important reason that different therapies are needed

for individual patients.

Today and tomorrow, we'll be referring to different seizure types. In the international classification of epilepsy seizures, the basic distinction is between seizures that begin in one part of the brain, which are termed partial onset seizures, and seizures that begin in wide areas of the brain, which are termed generalized onset seizures.

During several partial seizures consciousness is preserved, but complex partial seizures are those in which consciousness is impaired. Partial seizures can and frequently do spread quickly to involve the entire brain, thus culminating in a convulsion, a generalized tonic-clonic seizure.

There are several types of generalized onset seizures, including infantile spasms, which will be discussed tomorrow. Complex partial seizures are the

most common seizure type, affecting more than one-third of patients with epilepsy.

What is a complex partial seizure? The exact manifestations vary between individual patients, but a common denominator is a blank, unresponsive stare lasting one to two minutes. There may be automatisms which are meaningless, repetitive speech or movements. The frequency of these seizures varies widely. Some patients have them every day; other patients have them weeks or months apart. They progress at times to tonic-clonic convulsions in half of the patients. Although the seizures themselves are brief, there is a period of confusion lasting minutes to hours afterwards.

This is a video of a patient having a complex partial seizure with secondary generalization. She has given permission for use of this tape for educational purposes. What you'll notice is that she suddenly stops, stares, and remembers nothing from

this point forward. You see she moves her legs aimlessly. Those are called automatisms. At this point, she is unresponsive and unaware of her surroundings. She's not responding to voice.

So far, this is a complex partial seizure. However, the seizure now spreads to involve the rest of her brain. She cries out, arms and legs stiffen. This is the tonic phase of the seizure. Then the stiffening gradually gives way to jerking.

The so-called clonic phase of the seizure. The jerking increases in amplitude, slows in frequency, and eventually stops. She was sleeping and confused for several hours afterwards.

So this was a complex partial seizure, which spread to become a secondarily generalized tonic-clonic seizure. If we could stop the complex partial seizure, of course, this would also stop the progression to the convulsion. So these events, as you

can see, are dramatic, frightening to patients and family, and potentially dangerous to the patient.

Because the seizures are unpredictable, they have a severe impact on quality of life. This is a survey of patients with refractory epilepsy, which lists various aspects of daily life which they reported to be adversely affected by seizures. For example, many patients had difficulty with employment.

We may not think of epilepsy as being a fatal disease, but it is for quite a few patients. This is a Kaplan-Meyer plot of survival, comparing patients with chronic uncontrolled epilepsy to age and sex match controls. And you can see that the death rate in patients with epilepsy is accelerated compared to control groups.

Unfortunately, the treatment for epilepsy is often unsuccessful. Our goal, of course, is complete seizure control, but in

one study, 36 percent of patients with epilepsy were considered refractory, defined in this study as still having seizures after trials of two monotherapies -- that is two single drugs -- and at least one drug combination. And in clinical trials of many different new drugs for refractory epilepsy, only 20 to 50 percent of the patients achieve a 50 percent or better reduction in seizure frequency, and only a small minority become totally seizure-free.

You'll be hearing the term refractory often today. So let's take a minute to try to characterize what defines epilepsy as refractory. Refractory epilepsy is best defined by the numbers of drugs tried at adequate doses that failed because of inadequate efficacy, not because of side effects.

There's an emerging consensus among neurologists that a good operational definition is failure of two or more drugs

used alone and one or more drug combination. And two studies have indicated that in this circumstance, the chance of control with any current drug falls below 20 percent. So refractoriness is not defined by either the frequency or the severity of seizures, but really by drug resistance. It's possible to have infrequent seizures which are hard to control.

Well, what are our treatment options -- current treatment options for patients with refractory complex partial seizures? We can try combinations of several drugs. There's a device called the vagus nerve stimulator, which is an implantable device. It reduces seizure frequency in some patients, but rarely renders patients seizure-free. Brain surgery to remove the seizure focus is a good option for some patients, but only 3,000 to 5,000 patients per year undergo surgery in the United States, mainly because it's often impossible

to define the exact site of seizure onset, or because the site of onset can't be removed safely. And then finally, there are less commonly used drugs with greater side effect potentials.

Well, the other question is there are 10 or 12 commonly used anti-seizure drugs. So why do we need more? It has to do with the fact that epilepsy is not a unitary disease. There are multiple causes, which are probably based on different fundamental etiologies. And to address these varied etiologies, anti-epileptic drugs differ in their mechanism of action. And at this point, physicians cannot predict the most effective drug for a specific patient. So for a refractory patient, several different drugs and combinations are usually tried. However, the situation is not hopeless. Every time a new drug becomes available, some refractory patients become seizure-free.

The question will arise is it

worthwhile to keep trying new therapies in refractory epilepsy.

And the answer to that is yes. This is a study that related the number of drugs previously tried to the chance of becoming seizure-free with the next drug tried. And this is one of the studies I've used to define refractory epilepsy is the failure of two or more drugs.

The chance of success for the third or subsequent drug falls below 20 percent, but nevertheless, even after three or four drugs have been tried, it's possible to find a magic bullet that stops the seizures. So to quote the authors of this paper, no matter how many anti-epileptic drug therapies have failed, there's always hope of a meaningful clinical remission in this population.

Well, why should a new drug have a chance of controlling seizures in these refractory patients? That has to do with the fact the drugs are not alike. There are

several drugs. There are sodium channel blocks, and thus have an anti-excitatory effect. Some of the drugs affect post-synaptic GABA receptors and have inhibitory effects.

Some drugs seem to regulate neurotransmitter release. And then there are some drugs that have a mixture of these actions. Vigabatrin is the only one in its particular class. It's a GABA-metabolic blocker which increases REM GABA levels.

The other issue with these drugs, of course, is side effects. Although most of the adverse effects of anti-seizure drugs are not serious and they're dose-related, such as sleepiness or dizziness, it's important to know that all of our current drugs also have rare but potentially serious or fatal side effects. This is not a complete list, but this is some examples of such side effects for three of the older drugs -- phenytoin, carbamazepine, sodium valproate -- and for

six of the newer drugs.

However, even drugs with side effects may be useful. Felbamate is a good example. It's a drug that's used only for refractory partial epilepsy. It was approved by the FDA in 1993, and a year later, it was found that there was a 1 in 5,000 chance of liver failure, aplastic anemia, and about a 1 in 10,000 chance of death.

Nevertheless, this drug is still used. There have been an estimated 35,000 new patient starts in the U.S. between 1996 and 2006. This illustrates the usefulness of a specific drug for a small but critical segment of patients. And also, that patients may be willing to accept a significant risk of side effects to have a chance at better seizure control.

Well, this is an example of the category of patients for whom vigabatrin may be an option. This was a 35-year-old woman who had head trauma from an auto accident at

the age of 22, and then began to have staring spells, complex partial seizures lasting two minutes a year later. And at age 25, she had her first convulsion, and had several after that.

Phenytoin and carbamazepine therapies cause rash; topiramate caused confusion; a vagus nerve stimulator didn't work; oxcarbazepine reduced the seizure frequencies from five per month to two per month, but she eventually lost her job as a bank teller.

She was evaluated for surgery. She had a normal MRI, and a video EEG showed bilateral independent temporal lobe seizure onsets. And therefore, surgery was not considered a good option, and additional drug trials are planned. So even though this patient had infrequent seizures, they destroyed her ability to work.

So in summary, refractory epilepsy is a common problem. It degrades quality of

life. It's dangerous and it may be fatal. Complex partial seizures are often poorly controlled by current therapies. A favorable drug response to an individual drug is unpredictable in a particular patient, so we need a wide variety of choices of drugs, and especially those with different mechanisms of action and different side effect profiles.

Thank you very much.

I'll be followed by Dr. Chris Silber, who will discuss the efficacy and safety of vigabatrin in refractory complex partial seizures.

DR. GOLDSTEIN: Thank you.

Just to remind the sponsor, the FDA allotted 1-1/2 hours for all of these presentations, and we're well over, the way things are scheduled now, and I've just looked at the number of slides yet to come. So this is going to be a challenge. So please try to keep it succinct and to the point.

Thank you.

DR. SILBER: Good morning. I'm Chris Silber, and I'm vice president of clinical affairs at Ovation.

Today, I'll provide a brief summary of the clinical pharmacology of vigabatrin, and review the evidence supporting the efficacy -- its efficacy for the treatment of refractory complex partial seizures. I'll focus on the data from two pivotal U.S. clinical trials, and summarize the safety data from the clinical trial program. As FDA has indicated, Sabril has demonstrated efficacy as an adjunctive treatment for adults with partial seizures. We will still review the efficacy data to support the benefit/risk assessment.

Before I get into the specific efficacy and safety details in the clinical trial program, I'd like to provide a very high-level summary of what I'll be reviewing this morning. Specifically, vigabatrin

works. The two pivotal studies that I'll discuss today provide evidence of efficacy, and in particular, clinically meaningful benefits in seizure control. There are two safety topics that merit discussion in detail. First, the possibility that vigabatrin can cause MRI abnormalities in humans; and second, the peripheral visual field defect, which will be reviewed later.

This is a schematic of two CNS neurons and a synapse. The available evidence supports a unique mechanism for vigabatrin. GABA, represented in green, is an inhibitory neurotransmitter. Here, it is released from the presynaptic neuron, then it binds to a post-synaptic neuron with associated movement of chloride ions and hyperpolarization of the post-synaptic neuron.

Released GABA is taken up into surrounding glial cells, undergoes re-uptake, and is metabolized by the enzyme

GABA-transaminase, or GABA-T.

Vigabatrin blocks GABA-transaminase irreversibly, leading to an increased number of GABA molecules in the synapse, and it is the inhibitory activity of GABA that's considered to provide vigabatrin's anti-epileptic mechanism of action. Importantly, it is the only drug, as Dr. Faught noted, that has this unique mechanism of action, and represents an additional therapeutic option.

Now, turning to the findings of the clinical program, the pharmacokinetics of vigabatrin are straight-forward. It's nearly completely absorbed from the GI tract after oral administration; it has dose proportional and linear pharmacokinetics, and is not protein-bound. There is minimal metabolism, and greater than 95 percent is excreted in the urine as unchanged parent compound.

No significant effects have been noted related to food, gender, or race, and

no clinically relevant drug interactions have been observed. Clearance is faster and half-life shorter in infants as compared to adults. And finally, plasma concentrations are not helpful in monitoring vigabatrin efficacy due to its irreversible enzyme inhibition.

We're going to turn next to the evidence supporting the efficacy of vigabatrin as adjunctive therapy for the treatment of refractory complex partial seizures. This slide summarizes the design of pivotal studies 025 and 024, which support the efficacy of vigabatrin. In 025, after a baseline period to document seizure rate, patients were randomized and a parallel design, either to placebo or vigabatrin, added to their anti-epileptic drug regime.

Following a 6-week titration period, they were continued on that dose for a 12-week maintenance period. Study 024 was very similar in design to 025, with the only

difference being a four-week titration period. Importantly, this fundamental design is the same as that used in the assessment of the newer AEDs as adjunctive therapy.

This was not a first-line therapy trial design. Patients enrolled in the study were required to have failed an adequate trial of at least one AED, and were experiencing a minimum of six seizures per eight weeks during the baseline period.

In fact, the patients enrolled had previously been treated with a median of four or more classes of anti-epileptic drugs, and their prior anti-epileptic therapies represented multiple diverse agents and pharmacologic classes. It's important to note that these patients were quite typical of those enrolled in clinical trials of adjunctive therapy for refractory epilepsy, and representative of the population that will be treated if approved.

This slide summarizes the efficacy

results for the protocol-specified primary endpoint. Illustrated here are the median reductions for each of the treatment groups. As can be seen on the right, the three gram per day and six gram per day doses achieved statically significant reductions, 4.8 and 4 respectively, in seizure frequency versus placebo.

For Study 024, these are the data for -- again, the protocol-specified outcome measure of reduction in monthly seizure frequency -- for vigabatrin, three grams per day, a statistically significant reduction was illustrated versus placebo.

It's important to note that vigabatrin was associated with complete seizure freedom during the final eight weeks of the maintenance period for both studies. Complete seizure freedom represents a life-changing therapeutic outcome, and is the fundamental target of AED therapy. These results are particularly impressive given

that these were refractory epilepsy patients who'd received multiple prior AEDs and were still having on average more than two seizures per week at baseline.

In Study 025, about 12 percent achieved this important therapeutic target of complete seizure freedom at doses of three and six grams per day. In Study 024, similar results were seen, with seven percent of vigabatrin-treated subjects achieving seizure freedom.

Here is an analysis of efficacy onset for pooled data for the two pivotal studies. Among those patients that achieved a 50 percent reduction in seizures during the maintenance period, a substantial number can be detected by four weeks of treatment, and virtually all by six weeks of treatment. This rapid onset is important, particularly considering the PVFD that will be reviewed later.

These findings have been confirmed

by multiple clinical studies and in the literature.

Shown here are the efficacy results related to 50 percent reduction in seizures published in a 2008 meta-analysis by the Cochrane Collaboration. The data from the two pivotal studies I described are highlighted in yellow. For each of these publications, the vigabatrin versus placebo comparison is expressed as a risk ratio, with 95 percent confidence intervals.

Values to the right of the vertical dashed line representing a risk ratio of one are those with a favorable response to vigabatrin. As demonstrated here across multiple publications, the efficacy of vigabatrin in the treatment of patients with refractory CPS is supported.

I'm now going to review the safety of vigabatrin. The adverse event data that I'll describe was collected from pivotal studies 025 and 024, and the common adverse

event profile from these studies is representative of the broader safety database of 4,857 patients from 76 epilepsy studies.

In the pivotal controlled studies, the most frequent adverse events are listed on this slide. CNS-related events were the most common, consistent with that of other AED regimens. Of these, fatigue, somnolence and dizziness were more frequent in the vigabatrin-treated patients. These events were associated with discontinuation rates below one percent from these pivotal studies.

The events related to vision -- that is blurred vision and diplopia -- are also observed in association with the administration of other AEDs. These are quite distinct from the peripheral visual field defect that will be discussed shortly.

Here are the SAEs noted in the pivotal studies. Again, CNS events are noted on this list.

Apart from status epilepticus and

seizures, which would be expected in this population, and pneumonia, these events were only seen in one patient each. Similar to other AEDs, suicidality has been reported in association with vigabatrin use. And we will implement the FDA's new labeling recommendations. Outside of the pivotal trials and across all controlled and uncontrolled adult epilepsy patients -- 4,510 patients -- visual field defect was noted as the most frequently reported SAE, in 7-1/2 percent of patients.

I'll now turn to the topic of MRI abnormalities. It's important to understand the background on this topic and how we concluded there is no signal of MRI abnormalities attributable to vigabatrin administration in patients with CPS. As background, the histologic finding of intramyelinic edema, or IME, was noted in rodents and dogs. This refers to the occurrence of brain tissue findings of

fluid-filled vacuoles which can be reliably detected by MRI in these animals.

It's important to note that this finding is reversible. As a result, MRIs were included in subsequent trials of vigabatrin in CPS. These MRIs underwent two levels of central review, and there was no evidence of MRI abnormality attributable to vigabatrin exposure. However, in 2006, Dr. Phillip Pearl reported a series of three patients, all infants, who had a distinctive pattern of otherwise unexplained MRI abnormalities involving a high T2 signal, predominantly in basal ganglia and dorsal brain stem.

Although this report had the limitations of a case series, this finding renewed concerns related to this topic. Specifically, the FDA indicated that the radiologist who originally reviewed the studies may have focused too highly on white matter structures, when the animal findings

occur in both gray and white matter.

Ovation conducted a repeat review of these MRI films to determine if there were any areas of increased T2 signal regardless of location. The independent neuroradiologists reviewing the films were masked to prior treatment, study site, and the clinical history of the patients. There were over 600 patients in these prior trials, with over 2,000 MRI exams in the database.

Here are the results, with 95 percent confidence intervals of that re-review of MRIs from prior trials. No evidence of an excess of T2 abnormalities was seen in the vigabatrin-exposed subjects. The prevalence and incidence of MRI abnormalities were found to be similar in the vigabatrin-exposed and vigabatrin-naive population, and the anatomic distribution of these abnormalities was not at all suggestive of what had been recorded by Dr. Pearl.

In this re-review, they were

predominantly in the hemispheric white matter and were consistent with what has been reported in epilepsy populations in the literature.

So we concluded that the reassessment studies showed no evidence of MRI changes attributable to vigabatrin, and no evidence to suggest IME results from vigabatrin exposure in adults or children over the age of three treated for complex partial seizures.

In summary, vigabatrin has a unique mechanism of action. We agree with the FDA that vigabatrin has demonstrated efficacy in CPS. In addition, vigabatrin produces complete seizure freedom for some patients, which is a life-changing therapeutic benefit. Importantly, these effects can be detected within six weeks of initiation of vigabatrin.

Vigabatrin is generally well-tolerated, with a common adverse event profile similar to that of other

anti-epileptic drugs. A thorough re-review of MRI examinations from prior studies has shown no evidence that vigabatrin produces MRI abnormalities or intramyelinic edema in this patient population.

As I indicated, the most frequent serious adverse event is peripheral visual field defect, which will now be discussed by Dr. Robert Sergott.

DR. SERGOTT: Good morning. I am Bob Sergott, director of neuro-ophthalmology and professor of ophthalmology and neurology at Wills Eye Institute and the Thomas Jefferson University in Philadelphia.

This morning, I will be speaking to you about the evaluation of visual function, specifically peripheral field deficits and how ophthalmologists and neuro-ophthalmologists evaluate this clinical issue every day.

The purpose of my presentation is to increase your understanding about visual

field testing so that you can properly assess the data that you will see with vigabatrin. We know that vigabatrin can be associated with a peripheral visual field defect.

The vast majority of data indicate that visual acuity and color vision are not affected. We will explain to you the detection and monitoring of peripheral visual field defects requires regular assessments of visual function based upon the patient's testing ability. The defect found with vigabatrin is similar to that seen with mild to moderate glaucoma -- specifically, changes in the peripheral field without loss of central vision.

For all patients, including those taking vigabatrin, we must tailor our evaluations based upon the cognitive function and cooperation of the individual, especially when we use formal visual testing such as static and kinetic perimetry. In some cases, we will need to employ tests, like optical

coherence tomography and electroretinography, that provide objective, anatomic, and physiologic information about the visual system, and require little, if any, subjective input from the patients.

The peripheral visual field is defined as the environment that we see with our central vision fixed on a stationary target. The visual field also includes our central vision -- again, not affected usually by this medication. We can illustrate the peripheral by closing our left eye, looking straight ahead, and placing your finger about 90 degrees to the right. This area is the temporary visual field.

The field to the left of fixation can be tested by placing a finger approximately 60 to 70 degrees to the left of the fixation point, in the so-called nasal peripheral visual field. The peripheral field also extends 60 degrees above and 60 degrees below fixation. The visual field

simulator on the right illustrates how the topographic diagram of the visual field translates into a real-world setting.

The technique that we just discussed is called confrontation testing, and often provides us with an excellent estimate of a patient's visual field. This method of examination is taught to every medical student, as well as every ophthalmology and neurology resident.

We must now define a concentrically constricted field, as may occur with vigabatrin. The field deficit occurs concentrically, meaning the decrease develops temporally, nasally, superiorally, and inferiorally. We define the visual deficits that can be seen with vigabatrin as follows: With the mild defect, the field is narrowed to 120 to 160 degrees from the normal 180. With a more moderate deficit, the field is narrowed to 60 to 120 degrees.

And the final type of loss that may

occur in rare cases is a tunnel defect, where patients can only see within the central 60 degrees or less.

It is important to remember the constriction of the field does not occur in all patients treated with vigabatrin. Moreover, developing a mild deficit does not mean a patient's visual field will progress to a severe deficit.

Now we will describe the clinical methods that will be used to allow patients to benefit from the anti-epileptic properties of vigabatrin while best protecting them from developing severe field loss. Let's look at the methods used in the current practice of ophthalmology to measure the visual field. All these tests can reliably detect moderate visual defects that occur in glaucoma, as well as other optic neuropathies and retinal diseases. Testing the peripheral field is a process rather than an isolated event. The clinician has to structure the examination in

the best way for the individual patient. We have already demonstrated the first technique, confrontation testing, which can be performed by almost all patients. This simple technique is often the best method for some patients who have trouble with cognitively-oriented tasks, attention time, and ordinance.

The first quantitative test that we use for kinetic testing is called a Goldman Perimeter. With this device, we move a light of variable size and intensity from a non-seeing into a seeing area.

This test is easier to perform for the patient than any other quantitative field test. Goldman fields are available at most large ophthalmology practices, as well as tertiary care centers, especially those with residency programs in ophthalmology and neurology.

Static perimetry is the next method, and it involves increasing the

brightness of a stationary test light. This test is highly sensitive, and can provide very reliable information but is difficult for many patients to do, especially when there are deficits in cooperation and cognitive function. We'll discuss the details of statistic perimetry testing in epilepsy patients a little later, especially how we can still protect a patient's vision if they cannot reliably perform this test.

Approximately 20 percent of epilepsy patients are unable to perform a reliable field according to a study published in the year 2000 by Harding and co-workers. Given the varying cognitive abilities of epilepsy patients, this figure is not surprising.

However, we must remember that in ophthalmology and neuro-ophthalmology, we face this challenge every day with glaucoma patients and other patients. In fact, a study in Detroit and Toronto demonstrated

that only 25 to 34 percent of patients with glaucoma are able to perform -- I'm sorry, are unable to perform standard field tests, which represents a failure rate similar to that of epilepsy patients. Therefore, unreliable field testing in a small segment of patients is not a new or insurmountable problem for ophthalmologists.

As you just heard, some patients with complex seizures and infants treated with vigabatrin for infantile spasms will not be able to do any quantitative visual field examination. Fortunately for those patients, we can turn to electroretinography. In this test, the cells of the retina release tiny amounts of energy in response to a flash of light. If we know how much light enters the eye and how much electricity comes out, we could determine how the rods and cones are working, and the integrity of the retina.

To detect this electrical signal, the pupils are dilated and the patient placed

in a dark room so the maximum signal can be recorded. The tracing in black indicates the normal ERG, with an initial negative deflection, followed by a positive response. In some patients treated with vigabatrin, we'll see a decrease in the amplitude in the ERG response.

ERG expertise varies from medical center to medical center; however, standard protocols have been developed and are continually updated by the International Society for Clinical Orthophysiology of Vision to increase testing reliability.

Dr. Krauss and co-workers have correlated B-wave amplitude of the electroretinogram with a mean radius of the visual field using kinetic perimetry in some patients receiving vigabatrin. As you can see from the graphic representation of the data, the B-wave amplitude of the ERG decrease as the rays to the visual field become smaller.

Review of the literature discloses occasional discrepancies between visual field testing and ERG. We believe the lack of standardization of both the fields and the ERG contributes to these discrepancies. Therefore, ERG B-wave amplitude, and perhaps other parameters of ERG, may be helpful for patients who cannot do reliable field testing.

Optical coherence tomography is a newer technology to assess the structure of the retina. Here, we use light to produce marvelously detailed, anatomically accurate images to the retina, as seen in the accompanying slide. OCT produces images with a resolution now of six microns. We can see not only microscopic detail with this non-invasive, non-contact, painless examination, but we can also quantitate the thickness of the retinal nerve fiber layer and the overall macro thickness at one, three and six millimeters.

OCT is highly reducible and in wide use throughout the United States. The NFL denotes the normal nerve fiber layer. The ILM is the internal limiting membrane. GCL is the ganglion cell layer. We can see on the right side, the normal areas to the nuclear layer, and then down to the retinal pigment epithelium and choroid.

Ovation will be using OCT in its Phase IV studies to monitor not only the anatomic status to the retina, but also the status of the fibers from the retina that coalesce to form the optic nerve.

Realizing the challenge of detecting not only early visual field change but progression of field change, Ovation convened a group of five neuro-ophthalmologists, including myself, to establish parameters for the classification of the visual field loss and its impact upon daily activities.

We arrived at the following

classification. First, a mild defect with a retained field of 120 to 160 degrees. The group felt this change did not impact any of the patients' daily activities and was not clinically significant.

Next, moderate loss was defined as a retained field of 60 to 120 degrees. The panel again did not feel this would affect daily activities, except driving in certain states. It is important for you to remember that patients who could potentially benefit from vigabatrin are not driving because of their frequent seizures. Finally, severe loss was defined as a retained field of 60 degrees or less. Severe loss may be associated with the inability to walk safely in unfamiliar environments, and would require adaptive patient behavior.

Based upon the clinical expertise and standardized testing protocols, the panel believed that a mandatory safety program will be able to detect visual field loss of at

least the moderate level in all patients, and some patients at the mild level, to limit progression to severely constricted fields.

Let's summarize the reliability of the various testing methods to detect peripheral field loss and structural change in the optic nerve and retina. As you can see, kinetic perimetry, static perimetry, as well as ERG and OCT, may detect peripheral field and structure changes in many but not all patients. It's important to remember that all these techniques in the appropriate patients are very reliable at detecting visual field deficits of the moderate degree, consistent with our goal of preventing severe field constriction.

Now, as we discuss vigabatrin and its application for approval, we must consider that in the context of other medications with potential visual side effects that the FDA has approved. It is important to realize that the medications

listed here are commonly used, and that the ophthalmology community is both very familiar and very experienced with following patients for any toxicity of drugs ranging from chloroquine derivatives to oral contraceptives to chemotherapeutic agents and anti-infective medications.

For example, patients who are about to begin Plaquenil, a chloroquine derivative, are required to have an ophthalmic examination with special central 10-degree red visual field testing prior to treatment and every year on treatment. Vigabatrin will be administered under similar restrictions, as patients must comply with visual field testing in order to start and to continue treatment.

Therefore, monitoring patients for potential adverse effects of medication is an area of clinical practice that all ophthalmologists understand.

One study has been cited by the

Agency that reports mild visual acuity changes with vigabatrin. Several issues make this finding difficult to interpret. Visual acuity was not reported to be done with standardized luminants, as has been done in clinical trials with diabetic retinopathy, optic neuritis, and many other investigations.

No refractions were performed, as required for standardized clinical trials. A pinhole test done in this study is not a reliable substitute for an expert refraction. "Several older" patients reported to have mild cataracts, and finally, no central scotomas -- that is central visual deficits -- were detected with visual field testing.

Twelve of 32 patients had acuities ranging from 20/25 to 20/60, a level of vision that will permit these patients to read normal-size type, recognize faces, and drive in many states. Twenty of 32 patients

had acuity of 20/20 or better.

Now is the time to summarize where we stand with vigabatrin and peripheral field deficits.

First, I hope that the Committee understands that testing of peripheral vision is a clinical process performed by physicians with special training and expertise in the anatomy and physiology of the optic nerve and retina. It is not a single, isolated event. We know that some patients will develop peripheral field defects when their very severe, often life-threatening seizures, are treated with vigabatrin. However, we also understand that the field defects can be detected reliably at the moderate stage by a variety of tests, so that the benefits of this medication can be weighed against the risks of continuing therapy.

As with Plaquenil, ethambutol, corticosteroids, and many other medications, periodic ophthalmic examinations will ensure

the safest possible use of vigabatrin when seizures are not controlled by the currently available medications.

I will now turn the podium over to Dr. Steve Sagar, who will discuss the detailed characteristics of the peripheral visual field changes.

DR. SAGAR: Good morning. My name is Steve Sagar. I am a neurologist, and am the medical director for vigabatrin at Ovation Pharmaceuticals.

I'm going to discuss the data concerning our major safety issue associated with vigabatrin, the peripheral visual field deficit. I will first review the major features of the vigabatrin-induced peripheral visual field defect. I will then outline Study 4020, the largest, longitudinal study of vision conducted to date in patients exposed to vigabatrin. Based on that study and the extensive literature, I will give estimates of the prevalence and incidence of

the peripheral visual field defect and describe its severity and impact on visually guided behaviors.

The known risk factors will be reviewed. The time course of the peripheral visual field defect, and the data related to visual acuity will be presented. I will conclude with our recommendations for monitoring a vision. They are designed to minimize the occurrence of severe loss of peripheral vision, and to inform benefit/risk assessments.

In 1997, eight years after vigabatrin first went on the market in Europe, the first reports of constricted visual fields associated with vigabatrin appeared. These reports were consistent in finding that vigabatrin could cause a bilaterally symmetric, concentric peripheral constriction of the visual fields in some patients. The eight-year delay in recognizing this phenomenon is due to two

factors -- the peripheral visual field defect is asymptomatic in the large majority of patients, and it generally occurs only after years of drug exposure.

Reports were also consistent in finding that visual acuity is not affected. Rare reports of effects on acuity found the acuity to only be affected to a mild degree, accounting in part for the asymptomatic nature of the defect. The site of injury is the retina, as demonstrated by ERG findings of abnormalities of the inner retina; histopathology, although it's only reported in a single case; and imaging.

MRI fails to demonstrate lesions of the optic nerve or brain, and OCT demonstrates thinning of the retinal nerve fiber layer in established cases. The pathophysiology of the retinal injury is not known.

I will focus on Study 4020, the largest and most complete dataset we have.

This was a cross-sectional study with longitudinal follow-up and predominantly retrospective description of drug exposure. The 524 evaluable subjects were enrolled into three groups. Group 1 consisted of subjects who were taking vigabatrin at entry into the study and who had been taking it for at least six months.

Group 2 were subjects who had taken vigabatrin in the past but who had not taken the drug for at least six months. And Group 3 were subjects with no prior exposure to vigabatrin. They served as a comparison group.

The groups were further subdivided into children ages 8 to 12, and adults -- for the purposes of this study -- defined as greater than 12 years of age. Subjects underwent perimetry every four to six months for up to three years. The perimetry was either kinetic perimetry -- generally with the Goldman device -- automated static

perimetry, or both. The primary outcome measure was termed BCPC, or bilateral construction of the visual fields. This was a dichotomous designation based on central review of perimetries by a single reader, Dr. John Wild, who was masked to treatment.

This is the strength of the study, in that the perimetries were centrally reviewed by a consistent reader; however, there is a concern that there was no detailed protocol-specified definition of BCPC. Therefore, Ovation performed a post hoc quantitative analysis based on the 347 subjects who underwent Goldman perimetry.

Goldman perimetries were measured by an independent contract research organization for our analysis. The goal was to quantitatively define the extent of the peripheral visual field defect and to provide an objective determination of abnormality.

Study 4020 had a number of limitations. I've already mentioned that the

determination of BCPC depended on the overall assessment by a single reviewer. It was also expected that Group 3 subjects would begin vigabatrin during the study and provide truly perspective data, but only seven did so, and none developed a peripheral visual field defect.

There were few observations with short durations of vigabatrin exposure, and the specifications for perimetry techniques had to be relaxed during the conduct of the study in order to enroll additional sites. Subject selection and discontinuation may also impact data interpretation.

Despite these limitations, Study 4020 provides estimates of the prevalence and incidence of the peripheral visual field defect. Moreover, it provides information concerning the time course of the peripheral visual field defect, although it lacks the density of observations with short exposures to vigabatrin that we would like.

It also includes a large vigabatrin non-exposed comparison group of patients with epilepsy and taking other AEDs.

As a cross-sectional analysis, comparable to similar prevalence estimates in the literature, the percentage of subjects with BCPC on entry in the Study 4020 -- that is at the first conclusive perimetry -- was 28 percent, with confidence intervals shown on the slide. It is important to relate estimates of prevalence estimates to drug exposure.

This group had a median prior exposure to vigabatrin of 3.2 years. If one requires, as many vision researchers do, that an abnormal field be confirmed by a second examination, then the prevalence of confirmed BCPC in Study 4020 is 25 percent in adults.

The lower estimate of prevalence of 15.3 percent in children may be real or may be an artifact of the greater difficulty in testing children.

The group with the highest prevalence in Study 4020 were adults taking vigabatrin at study entry. They had a somewhat higher duration of vigabatrin exposure than other groups. Literature estimates vary widely, but cluster between 40 and 60 percent. There is an as-yet unpublished meta-analysis performed on behalf of the Cochran Collaboration -- by their calculation from 32 published studies, the overall median estimate of prevalence is 51 percent.

Based on Study 4020, the incidence of new BCPC is 8 percent per year while taking vigabatrin. That estimate is based on the data shown on this Kaplan-Meyer plot of the occurrence of BCPC in those subjects who entered the study with normal perimetries and who continued taking the drug. It assumes that the rate of development of BCPC is constant over the time of exposure.

I will now turn to the quantitative

analysis of Goldman perimetries from Study 4020 conducted by Ovation.

In our analysis, the outcome is not the occurrence of BCPC, but rather, degrees of retained temporal visual field. We used the temporal visual field as the primary measure, as one would expect that the total width of retained visual field would be the major determinant of visual function in daily life.

The total binocular field was calculated as the sum of temporal fields when both eyes were examined, and twice the temporal field when only one eye was examined.

The categories of peripheral visual field defect severity are the same as were used by Dr. Sergott in his presentation. This pie chart shows the severity of peripheral visual field defect at the final conclusive Goldman perimetry in Study 4020. By our definition, severe visual field

defect, the red slice, occurred in less than 3 percent of subjects; 83.5 percent of subjects retained more than 120 degrees of lateral vision at their final conclusive perimetry. The median retained binocular visual field in all vigabatrin-exposed subjects who had Goldman perimetry was slightly over 140 degrees.

This stack bar graph shows the distribution of severity of visual field defect as a function of duration of vigabatrin exposure. As can be seen with increasing drug exposure, the unimpaired category grows smaller and is replaced by higher degrees of severity.

Of note, although not illustrated here, there were only rare instances of rapid progression of the peripheral visual field defect. For example, there was only a single instance of a vigabatrin-exposed patient jumping from mild to severe impairment within one year of observation.

There are many comments in the literature that patients with a peripheral visual field defect are asymptomatic, but there is little formal data. 4020 provides systematic data concerning symptomatology. Subjects answered a 17-item questionnaire at each visit. The questions focused on peripheral vision, such as do you bump into doors or do you have trouble catching a ball? The frequency of answering yes to any one of 17 question is shown in this table as a function of the severity of the defect.

There is a high frequency of visual complaints in subjects with unimpaired vision, but positive responses increase with moderate, and most markedly with severe defects, although the number of subjects in the latter category are fortunately small.

The conclusion from these data, as well as from the literature, is that until peripheral vision is restricted to less than 120 degrees, the peripheral visual field

defect is generally asymptomatic.

The risk factors for peripheral visual field defect identified in Study 4020 are shown here. Duration of exposure, cumulative dose, and daily dose were all highly statistically significant in a univariate analysis, but obviously, they are not independent. The literature is generally consistent with these conclusions, although case series with small numbers of patients have not always confirmed these relationships.

In general, the visual field defect develops and progresses slowly. Although we do not have optimal prospective data describing the time course of the peripheral visual field defect, Study 4020 and the literature consistently find that the defect begins, and when it occurs, progresses slowly over months to years.

Those subjects with severe constrictions of the visual field have

generally had more than three years of drug exposure. In Study 4020, the briefest vigabatrin exposure of a subject developing a confirmed severe peripheral visual field defect was 2.9 years in a single subject, and all others had been exposed to the drug for more than three years.

This box of whisker plot shows the population data from subjects with Goldman perimetry in Study 4020. The retained binocular visual field is plotted against duration of vigabatrin exposure.

The boxes depict the underquartile range, and the whiskers, the overall range. Outliers are marked by orange dots. The green dots indicate cases that appear to be artifactual because of poor participation in perimetry or psychological overlay.

However, the main finding is that aside from the reduced variability with repeated testing, there is no apparent change in the distribution of these data over about

three years.

This slide shows group data of rates of change of retained monocular temporal vision for subjects while taking vigabatrin. As can be see, the average loss of visual fields in adults is less than two degrees per year. The average is similarly low in children, although 4 children with more than 7-1/2 years of exposure are the exception. We do not know if this is a real finding or whether it reflects again the difficulty of performing perimetry in children.

In general, a peripheral visual field defect cannot be detected before many months or years of therapy. There are only uncommon reports of a peripheral visual field defect being detected with less than one year of vigabatrin exposure.

I've summarized the reported cases from clinical trials in this table. In Study 4020, there were 58 vigabatrin-exposed

subjects who had perimetry performed with less than one year of vigabatrin exposure. Five were found to have BCPC -- one after 9 months of exposure and four after 11 months. The case from Study ROO3 called out in the FDA review was a woman with six visual field examinations, one of which was read as normal and the others, one of which preceded her first dose of vigabatrin, showed a superior defect.

I will return to the pooled cohort analysis shortly, but note that of 104 subjects examined with less than one year of drug exposure in that cohort, only two were found to have peripheral visual field defect.

I need to say a word about the pooled cohort analysis, a study upon which the FDA reviewer put a great deal of weight. This was a cross-sectional study of perimetries performed in subjects who participated in clinical trials of vigabatrin and other AEDs at multiple international

sites. As the reviewer correctly points out, Ovation does not discuss this study in detail in our NDA submission.

The reason is, we do not consider the study to be especially informative. It is a cross-sectional study and gives estimates of the prevalence of peripheral visual field defect of 31 to 36 percent, quite consistent with other cross-sectional studies reported in the literature.

However, the perimetry methods of the study are not specified. The visual field grading system is ambiguous, and the incidence analysis is seriously flawed. We do not have access to the primary data and cannot perform a valid data analysis, so we believe the study has very little value. Hence, we did not discuss it in our NDA.

I will reemphasize, however, that whereas the FDA reviewer cites this study as evidence for the frequent occurrence of visual field defect with less than one year

of exposure to vigabatrin, in the pooled cohort analysis, only 2 of 104 subjects who were examined with one year or less of drug exposure actually developed a visual field deficit, quite consistent with the findings of Study 4020 and with the literature.

Five additional cases of peripheral visual field defect with less than one year of drug exposure I could cull from the literature are listed on this slide. In general, with literature cases, we do not know how many of the subjects were actually examined with less than one year of exposure. Exceptions include the Schmidt study, which was a prospective study in which all 29 subjects had periodic perimetries during their first year of exposure.

The Fechner study, listed at the bottom of the slide, was not in epilepsy but was in stimulant abuse. It did, however, carry out baseline and systematic follow up perimetry examinations and found no changes

in vision either during or one month following an eight-week exposure to vigabatrin.

In the post-marketing experience, there were six reports of possible cases of peripheral visual field defect with less than one year of drug exposure.

A young woman -- one case was well-documented. A young woman developed constriction of her visual field after five weeks of vigabatrin exposure, but this reversed back to normal within two months of stopping drug, so it did not represent a permanent deficit.

A key question is whether vigabatrin can be -- whether a peripheral visual field defect can begin or worsen once drug is discontinued. Again, Study 4020 and the literature are consistent in that the peripheral visual field defect is stable after discontinuing drug and neither worsens nor improves to a substantial extent.

These are group data, again, from Study 4020 based on Goldman perimetry of rates of change of monocular temporal visual field after stopping vigabatrin. For comparison, the rates of change for Group 3 subjects without any vigabatrin exposure are also tabulated. On average, there is no progression after vigabatrin is stopped.

The preponderance of evidence supports the conclusion that vigabatrin does not have a major impact on visual acuity. The reports of exceptions as noted by Dr. Sergott are confounded by other factors, including failure to refract the subjects for their examinations, and especially in earlier reports, failure to distinguish reversal of pharmacological effects of the drug from permanent effects.

The data on this slide are from a study from the University of Glasgow following patients on vigabatrin and other anti-epileptic drugs with serial visual

testing. As you can see, there's no difference in the visual acuity between the vigabatrin-treated subjects and those exposed to other types of anti-epileptic drugs. Their findings are quite similar for color vision.

These findings are supported by very consistent reports from the literature that overall vigabatrin exposure has no defectable effect on visual acuity. The major studies from the literature are shown here. The exception is the study by Miller, et al., in which subjects were still taking vigabatrin at the time of the examinations, and as was mentioned, were not refracted for acuity testing. Even if the low acuity values ranging from 20 to over 25 to 20/60 represent an effect of vigabatrin, the effect is modest in degree.

The data that I have presented here have clear implications for patient management. The asymptomatic nature of the

peripheral visual field defect means that it has minimal impact on visual function in daily life, but it also means the patients do not recognize the problem and spontaneously report it to their physician. Therefore, Ovation recommends that patients taking vigabatrin undergo regular monitoring of visual function.

Ovation guidelines for monitoring vision are summarized on this slide. They are generally consistent with international guidelines, such as those from the Royal College of Ophthalmologists, and with recommendations for the European and other markets.

About 80 percent of patients with epilepsy can be followed with perimetry. We recommend routine monitoring every six months in adults. An abnormal perimetry should be promptly confirmed by a second test, and should trigger an increase in the frequency of monitoring to every three months.

Study 4020 indicates that physicians and patients will comply with this schedule. Quantitative perimetry can be challenging in this patient population, and testing methodology must be tailored to the individual patient. ERG and optical coherent stemography provide alternative methods when reliable perimetry cannot be performed.

In summary, the great preponderance of evidence is that vigabatrin does not impact visual acuity. However, vigabatrin is associated with a distinctive bilateral constriction of the visual fields in some patients who take it. In only a small percentage of those who develop a peripheral visual defect will it become sufficiently severe to influence daily life.

The time course of development and progression of the peripheral visual field defect in the large majority of patients is slow, occurring over months. This means that adequate benefit of vigabatrin on seizure

control and quality of life can be demonstrated before a major risk of loss of peripheral vision is incurred.

For patients who choose to discontinue vigabatrin, their visual field will remain stable. Effective methods of visual monitoring exist to identify those patients who may be especially susceptible to the retinal effects of vigabatrin and to inform periodic benefit risk assessments.

I would now like to call on Dr. Cunniff, who will discuss the REMS plan.

DR. CUNNIFF: I will be presenting an outline of our proposed risk evaluation and mitigation strategy, or REMS, for Sabril.

Since the submission of the briefing document for this meeting, we have incorporated additional elements to ensure safe use based on feedback received from additional stakeholders, including the FDA reviewers, by reviewing their briefing document. You heard today that refractory

complex partial seizures is a serious and life-threatening disease, and that a significant unmet medical need exists for patients with this condition. The proposed REMS that I will outline today will ensure that a favorable benefit/risk profile is maintained for Sabril during marketed product use.

The primary goals for the Sabril REMS are shown here. The first goal is to minimize the risk of a Sabril-induced PVFD while delivering maximal benefit to the appropriate patient populations. For patients who benefit from Sabril and continue treatment, our second goal is to detect the PVFD before it results in a clinically meaningful restriction in a patient's peripheral vision.

You heard from Dr. Sergott earlier about the number of ophthalmologic tests available to specialists to accomplish this goal for most patients before progression to

a severe peripheral vision restriction occurs. Finally, our third goal is to ensure regular ophthalmologic monitoring to facilitate ongoing benefit/risk assessments between educated physicians and informed patients and/or their caregivers. These monitoring recommendations have been employed throughout the world for nearly two decades now, and our REMS will ensure that the appropriate benefit/risk discussions occur on a continual basis while a patient is receiving Sabril.

Sabril's REMS involves all types of risk management tools, namely a patient/caregiver medication guide that addresses the risk of both PVFD and MRI abnormalities in patients with infantile spasms; a communication plan that also addresses both PVFD and MRI abnormalities consisting of physician and patient or caregiver educational programs; and finally, many restrictive and enforced elements to

ensure safe use. The REMS elements will be implemented through our branded program called SHARE, which stands for Support Health and Resources for Epilepsy.

I will now elaborate on the three categories of the REMS tools. The purpose of the medication guide is to provide information to the physician, patient, and/or their caregiver about the risks associated with Sabril therapy, including the risk for a peripheral visual field defect, MRI abnormalities in patients with infantile spasms, and the AED suicidality.

The medication guide is written in patient-friendly language, and is reviewed and discussed with the patient and/or their caregiver multiple times during the drug prescribing and dispensing process. The medication guide is also provided to the patient or their caregiver each time Sabril is dispensed.

The communication plan and

educational programs include a comprehensive set of targeted education and outreach tools. Physical education tools will include the following: The Sabril package insert, with a prominent black box warning highlighting the risk for PVFD and a separate warning highlighting the risk for MRI abnormalities in patients with infantile spasms; a Dear Healthcare Professional letter will be issued upon approval that reinforces information on the approved clinical indications, the benefits and risk of Sabril, including PVFD and MRI abnormalities.

A Sabril benefit/risk slide presentation will also highlight the PVFD and MRI safety issues, and visual testing guidance will be published and available.

Patient education tools include the medication guide I just mentioned. It will also include a physician-patient agreement that can be used to reinforce a patient's understanding of the benefits and risks of

Sabril therapy, including the risk for PVFD and MRI abnormalities in patients with IS.

We recommend that this agreement be reviewed with the patient before starting treatment, and during the early evaluation of Sabril therapy. Brochures containing information on epilepsy and PVFD associated with Sabril will be available on a special Sabril product website that the patient can access, and we will also provide a web-based visual simulator so the patient can understand the potential for PVFD and what that may mean on their quality of life.

The controlled drug distribution system, with a central call center and a network of select specialty pharmacies, is at the core of implementing elements to ensure the safe use of Sabril. We will target physicians with experience in treating epilepsy, and the initial prescription for Sabril can only be written by board-certified neurologists. This is the single risk

management tool in place in Europe.

In order to prescribe Sabril, the physician must undergo education utilizing materials contained in the communication plan I just discussed. After completing this education, the physician must attest to having experience in treating patients with epilepsy, and having an understanding of Sabril's approved clinical indications, risks, and the recommendations for visual testing.

Following attestation, the physician is then registered into SHARE, and only then can register patients into the program. Sabril will only be dispensed if all requirements for physician and patient registration are satisfied.

Before a patient can receive Sabril maintenance therapy, a mandatory benefit/risk assessment is performed to ensure that patients without clinically meaningful improvement in seizure reduction or spasm

control are discontinued from therapy. Sabril dispensing will be limited to a few select specialty pharmacies, which compromises a controlled drug distribution system.

A visual testing reminder system will be available to help patients complete regular ophthalmologic testing, and those who cannot comply will be removed from drug therapy after a 45-day grace period. All patients will also be registered into a mandatory Sabril registry, and data from this registry will be reviewed, analyzed, and submitted to the FDA on at least an annual basis.

The schematics shown here further elaborate on the enforced benefit/risk assessment for patients with CPS and IS, and the enforced ophthalmologic monitoring provisions for those patients with CPS. There is no enforced monitoring provision for the patients with IS, since visual testing in

this population requires a risk/benefit assessment for each patient, since ERG is performed under sedation, which carries a procedural risk for infants.

After therapy with Sabril is initiated, there is a three-month evaluation phase. Before a patient with CPS or IS can receive maintenance-based treatment, a mandatory benefit/risk assessment is required. Those without clinically meaningful improvement in seizure reduction or spasm control will be discontinued from Sabril therapy, since no additional prescriptions will be allowed.

Approximately 45 days prior to required ophthalmologic testing, the SHARE call center will remind patients to complete their appointment. If an appointment is missed, the patient, their caregiver, and their physicians will be informed that required testing must be completed within 45 days. Those patients with complex partial

seizures who fail to comply will be discontinued from Sabril therapy since additional prescriptions will not be dispensed.

All data collected and entered into the SHARE database will form the basis of a mandatory Sabril registry. The registry will collect prescriber specialty and practice setting information, and will also collect patient demographics, diagnoses, prior and concurrent anti-seizure medications, effectiveness as measured by the proportion of patients responding to Sabril during the treatment initiation phase, and all ophthalmologic testing data that was collected for CPS patients -- to allow for additional terminations of the frequency, onset, severity, and progression of the PVFD.

Ongoing analyses of data entered into the SHARE database and into the Sabril registry will also form the basis for periodic assessment of the effectiveness of

Sabril's REMS. Data from the Sabril registry will be analyzed and summarized to the FDA on an annual basis. Knowledge added to behavior surveys of physicians and patients or their caregivers will also be performed during the first, second, third, and seventh post-marketing years, to assess compliance with REMS requirements.

Pharmacovigilance information, including spontaneous adverse event reports and literature reports, will be evaluated quarterly for three years and annually thereafter. In addition, all serious liver injury cases will be submitted to FDA on an expedited basis per the Agency's recent request. Results of REMS assessments will be discussed with the FDA, and modifications to the program will be made as appropriate.

Risk management is an ongoing iterative process involving all stakeholders, and we will actively work with the agencies, patients, physicians, and caregivers to

ensure that the REMS is effective in supporting the safe use of Sabril. We believe that the proposed REMS will minimize the risk for a Sabril-induced peripheral visual field defect, while delivering the maximum benefit to the appropriate patient populations.

I would now like to invite Dr. Roger Porter to assess Sabril's benefit/risk profile, and conclude our presentation.

Thank you.

DR. PORTER: Good morning. I'm Roger Porter from the University of Pennsylvania and the Uniformed Services University.

Today, I will discuss the risk/benefit assessment for vigabatrin in complex partial seizures. I will divide this presentation into three fundamental parts. First, we will talk very briefly about refractory complex partial seizures as a devastating disorder.

Next, we will talk about vigabatrin

and its important benefits. And finally, we will talk about vigabatrin's risks, and how these risks can be effectively managed.

As you have seen from Dr. Faught, vigabatrin is effective against complex partial seizures, the major uncontrolled seizure type in adults. Vigabatrin is indicated for those patients with CPS who have not responded adequately to medications, but we expect that only a small subset of these difficult-to-control patients will be candidates for vigabatrin.

The risk for morbidity and mortality with complex partial seizures is substantial. The mortality rate in patients with medically refractory seizures can be four to seven times higher than the general population, and injury rates can also be substantially higher. This morbidity and mortality profile is even worse when the seizures are poorly controlled.

Refractory patients with frequent

seizures have a decreased quality of life compared with those with fewer seizures. Refractory patients also have an increased risk of accidents and injuries, suicide, and sudden unexpected death in epilepsy, as you have already heard. Clearly, therefore, patients with poorly controlled complex partial seizures suffer greatly from this disorder.

As you know, the current state of treating patients with refractory epilepsy requires that doctors recognize that some drugs will work better than others in individual patients, but predicting this responsiveness for a specific drug and a specific patient is very difficult. And as you have already heard, the physician essentially uses a trial and error method in choosing the medications.

Now let us look at the benefits of vigabatrin. In addition to its novel mechanism of action, here are the benefits of

vigabatrin as add-on therapy. First, there are substantial numbers of patients who respond to vigabatrin. Also, some highly refractory patients experience a significant reduction in seizures, as documented in clinical trials. Some may even become entirely free from seizures. Vigabatrin is generally well-tolerated, and as with most anti-epileptic drugs, the dose-related adverse effects are related to the central nervous system.

Finally, let us take a look at the risks. Peripheral visual field defect, or PVFD, is a well-characterized condition, and we know how to monitor for the emergency of this abnormality. In Study 4020, 2.4 percent of vigabatrin-exposed patients with a PVFD had a severe loss of visual field. However, an opportunity exists to evaluate efficacy early, thus limiting patient exposure to risk.

This slide is designed to give a

sense of the timeline related to treatment of refractory complex partial seizures and the onset of visual field abnormalities.

First, most patients can be evaluated for the efficacy of vigabatrin in a three-month period. If the drug does not improve seizure frequency in this time period, then further efforts with this drug will probably not be useful and the drug should be discontinued. With regard to the probability of the timing of the onset of a PVFD, of course, we have no definitive data. We do know that for CPS, the earliest report of any type is two months; the earliest report in our 4020 clinical trial occurred at nine months; and the overall median first appearance is after several years.

Therefore, an opportunity exists to evaluate the efficacy of vigabatrin in individual patients early in vigabatrin therapy, since the risk of PVFD increases over time. As an example, physicians can

take three months to initiate and evaluate the new drug. After this three-month period, we will make a determination from the standpoint of efficacy and safety of whether we should continue the medication. Remember that even for those that remain on the drug, only 40 to 60 percent will ever develop a field defect.

To summarize the benefit/risk, therefore, we know that vigabatrin is an effective treatment option for complex partial seizures, and we've seen that the evaluation time window gives us the opportunity to test for a clinical response during a period of minimal risk for PVFD. For most patients, the risk of uncontrolled complex partial seizures outweigh the risks of the potential adverse effects of vigabatrin.

Therefore, the benefit/risk profile favors a trial of this drug as adjunctive therapy for adult patients with refractory

CPS who have inadequately responded to alternative treatments. Given the severity of partial seizures with attendant substantial morbidity and mortality, and given that vigabatrin is a drug that can effectively and safely treat this condition, I respectfully submit that the important clinical benefits of vigabatrin should be made available to our patients with epilepsy.

Thank you.

I will now turn the podium over to Chris Silber, who will address your questions.

DR. GOLDSTEIN: This is a time for the Committee to be able to ask clarifying questions from the sponsor, who I want to thank for being right on the money. Just for the Committee's information, the way I do this is, the questioners are allowed to ask questions in the order in which they are received, and what I try to do is if somebody hasn't asked a question and wants to and somebody already has asked a

number, I try to let everybody have their chance to ask.

So we have 15 minutes now for clarifying questions. Let's see.

First, I guess it's Dr. Gardner.

DR. GARDNER: I have a question for Dr. Cunniff about the practice -- it isn't clear to me who is treating these patients, particularly outside of metropolitan areas. Can you tell me what proportion of the refractory patients are likely to be seen by family physicians?

Also related, what's the importance in therapy of continuation -- continuity of care? So if you give a -- if you're requiring an ophthalmologic monitoring and you give people 45 days to get in and get it and they don't -- but they do it at 60 days, in the meantime their therapy is cut off, what does that do to the progression -- I mean, I'm sorry, the maintenance of the effect?

DR. CUNNIFF: Sure. I'll answer the second part first, and then I'm going to ask our clinicians to answer the first part.

With respect to tapering the patient off the medication, we did build in a cushion there, because we realize getting in and out of the testing center may not always go according to plan. So what we hope to do is -- you know, 45 days before the test is due, we send out a reminder so the patient knows they need to get their test done. If it's not done when it's supposed to be done we send out another reminder within five days, and we also let the caregivers know that unless this test is done within the 45 days, the patient is going to need to taper off the therapy.

So I think by highlighting it, threatening withdrawal of the drug, I think both the ophthalmologist, the neuro-ophthalmologist, the neurologist is going to make sure that their patient gets

tested. And that's really the point of the program.

I think I'll ask Dr. Faught or Dr. Porter to maybe discuss how these patients would be treated in the community setting.

DR. FAUGHT: This drug, practically speaking, is going to be used in tertiary care centers. It's going to be used in epilepsy centers primarily. I'd be very surprised if any family physicians would use this drug. First of all, we're going to require that only neurologists can prescribe the drug. The training program involved will require certain certifications. That's pretty much the way it's going to be distributed. I don't think that it's going to be a problem with people who are not familiar with epilepsy using the drug.

DR. GOLDSTEIN: Thanks.

Dr. Crawford, next.

DR. CRAWFORD: Thank you, Mr. Chair. My question is for Dr. Silber. A very quick

question.

Dr. Cunniff, while you're there as he's coming up, it wasn't clear for me, when you talk about peripheral field vision defects, is it typically both eyes or could it be one or both eyes?

DR. CUNNIFF: So to comment on peripheral visual field defect, I'd ask Dr. Sergott to describe presentations of the field defect.

DR. CRAWFORD: Thank you. But my question is very quick. Is it typically one eye or two eyes involved?

DR. SERGOTT: It's always two eyes.

DR. CRAWFORD: Thank you very much.

For Dr. Silber.

DR. SILBER: Yes.

DR. CRAWFORD: I just ask that you clarify your slide 21 please. The one -- it was related to the MRI repeat review process.

DR. SILBER: Yes.

DR. CRAWFORD: Did you say that the

conclusions were based -- you concluded there were no MRI abnormalities in patients over age three -- so my question was, were there any subanalyses for infant film reviews?

DR. SILBER: Infants were not included in this cohort. This was a re-review of data that had previously been reviewed by the prior sponsor. This included patients with complex partial seizures. Both children and adults were included in that cohort. There were no infants included in that set.

No.

DR. GOLDSTEIN: Thank you.

Dr. Vega.

I'm sorry. I lost track.

Dr. Kramer.

DR. KRAMER: I have two questions. First, you stated -- these are both about the REMS program.

You stated that a board-certified neurologist would be required to initially prescribe medication. Could you clarify

whether or not, for refill prescriptions and continued maintenance, it would also require the involvement of a board-certified neurologist? And then I have another question, but maybe you can answer that first.

DR. CUNNIFF: Yes. What we're going to require is the initial prescription be by a board-certified neurologist, and we will cross-check that against the list that we obtain from the certification board. I think after the initial prescription is done, there may be some instances where someone is board-eligible or the patient is on vacation and it was an emergency prescription written to cover that -- then we have the attestation program, that that physician to prescribe Sabril medication must also attest that they have experience in treating epilepsy.

We would restrict the whole entire process to epileptologists, but there's no certification as of yet for that

subcommittee.

DR. KRAMER: But I presume from what you're saying that you would not allow primary care practitioners to prescribe maintenance prescriptions?

DR. CUNNIFF: If they had experience in treating epilepsy and if the initial prescription and determination was written by a board-certified neurologist, that would be allowed.

DR. KRAMER: And second question, also about the REMS program, ultimately if this is approved and the REMS program is implemented, a lot of the communication is fundamentally dependent on what your company issues in terms of communication.

And I was struck several times in the presentations on your focus on average effects. For instance, the statement that on average, there's -- well, anyway, I can't locate it right now, but there was a real focus on average effects. And my question

is, don't you think that for communicating to patients, it's required that you emphasize the range of possibilities that can happen? For instance -- actually, the example I was thinking about was after the drug is discontinued, can there be continued worsening or appearance of visual field defects. And in our background packet, it appeared that there were cases where that had happened. And yet you focused on on average, this doesn't happen.

Could you comment on that, please?

DR. CUNNIFF: Yes, I think it's a really good point. I agree with -- we should focus on putting everything in perspective so the outliers, we should be addressing those to let people know that it's a possibility that it could occur very early on. I don't want to preclude the -- for example, looking at onset, I don't want to give a false set of assurance that it's not going to occur very early on. It could in very rare circumstances. I think we need to

discuss the outliers, and we need to put all the data into perspective. I think the labeling that we'll negotiate with FDA both for the physicians package insert and the medication guide will reflect that, and those will make it into the communication materials.

DR. GOLDSTEIN: Dr. Vega?

DR. VEGA: Yes. My question is for Dr. Cunniff, too. It's related to communication. What did you mean by patient-friendly language?

DR. CUNNIFF: What we want to do -- the medication guide is a FDA-mandated tool. A mandated tool for many drugs, including I'm sure, for Sabril.

And it puts the risks of the peripheral visual field defect and some of the MRI abnormalities into language that the patient could understand. This is very common in Europe. We have a number of drugs in Europe, and what we do there is we do readability testing. So we kind of write a

label and then we have a CRO that evaluates it and makes sure patients can understand that. So we'll do the same thing here to make sure that the risks we're trying to convey are understood by the patient.

DR. VEGA: I didn't see anywhere in your presentation anything related to patients who might not speak English. How are you going to address those issues?

DR. CUNNIFF: Very good question. We typically have materials in Spanish for Puerto Rico and some of the other territories in the southwest.

And I think we would, at minimal, have Spanish language information as well.

DR. KATZ: I think you said the median number of anti-convulsants that patients failed on prior to enrollment into the controlled trials was about four, I think.

DR. CUNNIFF: The median number of drugs they had previously been exposed to.

DR. KATZ: Right.

DR. CUNNIFF: Not necessarily previously failed.

DR. KATZ: Okay. So my question is, can you talk a little bit about what sort of criteria were used to decide that they weren't responding well to those drugs in the past? And the other question is have you looked -- have you analyzed the data for those patients -- for patients who didn't do well prior to entry into the study on four or more drugs. It's not a randomized subset. I understand that. But there are a fair number of them, and you could get some sense of whether or not efficacy persisted in those patients who really didn't do well on many drugs.

DR. SILBER: First, with respect to the criteria that were utilized, we collected information -- in addition to information tabulated in case report forms regarding numbers of prior drugs exposed -- those existed as data. With respect to prior failure of adequate therapy, these were captured from the case

report form, so the precise methods that were utilized were simply not known other than the clinician reporting that these patients had been exposed to drug and had failed due to efficacy. We also had information in some cases where there were side effect failures.

As a very high-level summary, this chart is summarized for both of the pivotal studies -- 024 on the left and 025 on the right. For each of those studies, placebo and three gram a day for the 024 study; placebo, three and six gram. We've left out the one gram a day dose. What can be seen is that for both categories, one to three failed prior drugs, or four to six failed prior drugs, the basic treatment group difference is maintained for the three gram and six gram a day dose.

DR. GOLDSTEIN: We're at our scheduled -- just about our scheduled break time, but I have 10 Committee members that had qualifying questions to ask. So let's go five

minutes into it. Remember that we will be discussing all these things in detail again later. But let me just go through the list and allow people to have a chance to ask these questions.

Dr. Snodgrass?

DR. SNODGRASS: Regarding monitoring sensitivity (inaudible) the issue of mild versus moderate or even severe PVFD, how you're able -- it appeared from what he said that you're able to pick up the moderate but maybe not the mild quite as easily. How will you address that? Not only maybe increased frequency. I'm thinking of the younger age group -- below age six, for example. How would you pick that up -- more mild cases? Because this relates -- not only monitoring sensitivity and monitoring frequency, but also the number of responders and non-responders are going to be fairly low. So there's got to be some sort of balance here.

DR. SERGOTT: I think this is a very

important issue for the Committee to understand.

And the overall question is not just for vigabatrin. It's for every optic nerve disease or every retinal disease where visual fields are important. So if we take your six-year-old first, that patient will do confrontation testing, probably do a Goldman field with some training and repeated efforts, and we'd probably be able to do an OCT eventually. But may not do that well with static perimetry.

So as a clinician, if I were taking care of that youngsters, come in, confrontation fields, talk to the mother and father about visually-oriented behavior, tell them what to watch for, see how they did the first time with Goldman fields. And then a lot of visual field accuracy depends upon the time spent with educating the patient. And that's true whether it's six or 60. And the mild, moderate, or severe that you ask about is a reflection again of what we know from

other diseases of the optic nerve, especially glaucoma, about what is the sensitivity of the testing method.

So we're not going to say we can detect every mild deficit with vigabatrin. We'll detect a few. The moderate ones, we can detect that because we detect that in glaucoma, ischemic optic neuropathy, optic neuritis, brain tumors.

DR. GOLDSTEIN: Dr. Chugani.

DR. CHUGANI: Yes, I've got a quick question about the dosage -- the six gram versus the three gram. I thought I saw a study from Yale that used amos spectroscopathy (?) to measure a dose response curve with vigabatrin in normal adults, and showed that at three grams, you basically reached a plateau.

DR. SERGOTT: I'm not familiar with that particular study. The Study 025 was undertaken to explore a dose range and included one, three, and six grams per day. As you saw, the efficacy associated with six grams a day was

quite substantial. However, the optimal dose was identified as three grams a day, largely on the basis of the side effect profiles.

DR. CHUGANI: Yes. Basically, that was a dose response curve. They measured using high field short echoes. The concentration of GABA using proton spectroscopathy and showed that. And they did a classical pharmacological dose response curve, and showed that at three grams in normal volunteer adults, it plateaued off. And their recommendation was it made no sense to go beyond three grams.

DR. SERGOTT: Correct. And I just wanted to mention, we do note that in our labeling that there is a plateau effect at three grams a day. There's no increase in efficacy at the six gram dose, but there is an increase in side effects. So we're cautioning people don't go above that typically.

DR. GOLDSTEIN: Dr. Mizrahi.

DR. MIZRAHI: Thanks. Question about monitoring. The proposed plan is for initial

monitoring at six months. And if the initial ranges have been reported to be two to nine months, why are we looking at six months rather than -- let's say an earlier monitoring at three months or something earlier? And then a related question is about the ERG. Are you considering the ERG to be a specific test for visual field disturbance, or are you considering it a secondary surrogate? And if you're thinking of it as a surrogate, how well do those studies match up with true visual field defects?

DR. SERGOTT: To comment on both of these, I'd ask Dr. Steve Sagar.

DR. SAGAR: In answer to your first question, the monitoring recommendations were based on experience with the European market, where our monitoring recommendations are in line with those with the recommendations of the Royal College of Ophthalmologists, and with the data that shows that onset of detectable visual field defect with less than one year of exposure is an unusual occurrence.

Where our monitoring recommendations diverge from the European recommendations and from the Royal College of Ophthalmologists is that we recommend that if an abnormal test is found, that the frequency of monitoring at that point should increase to every three months. This is an effort to balance what we think patients and physicians will comply with, versus a reasonable monitoring approach to try to detect visual field deficits before they become severe and impact quality of life.

In answer to your second question about ERG, we regard ERG as a predominantly confirmatory test, and a test to be used in cases where perimetry cannot be performed because of the patient's cognitive status or other factors.

DR. GOLDSTEIN: Thank you. Given biology being what it is, I think we are going to need to stop now. I do have a list of several Committee members that wanted to ask

questions. What we'll try to do is after the FDA presentations, we'll try to pick these up. The sponsor is obviously going to be here for the whole time, and we'll try to make sure that everybody asks the questions that they'd like to.

Thanks. Ten minutes. Back at 10:30 on the dot.

(Recess)

DR. GOLDSTEIN: Okay. Next up are the FDA presentations. Please, let's come to order.

Next up are the FDA presentations. The first is by Dr. Farkas.

DR. FARKAS: Good morning. I'm Ron Farkas, from the Division of Neurology Products at FDA.

The talk today is about ophthalmic findings from vigabatrin in adults. And although I'll touch on findings in children a little bit, that talk will mostly be tomorrow.

In 1998, FDA issued a not

approvable action for vigabatrin based on visual adverse effects, and the FDA asked the sponsor to characterize the visual adverse effects and to describe how to monitor for these effects and prevent them.

Again, this first presentation is about adults with complex partial seizures for NDA-20427.

This talk will address the location, and in particular, discuss if the adverse effects are limited to peripheral vision or if there might also be effects on visual acuity. The talk will look at severity -- mainly severity regarding peripheral vision, because that's where there's available data.

I'll also touch on functional effects and visual disability in patients; reversibility and stability; time to onset and speed of progression; dose and time effect; and monitoring and prevention.

There are shortcomings -- serious

shortcomings with the data that I'd first like to talk about. Most of the available data is from cross-sectional studies and case series.

FDA finds that these studies -- that this data is susceptible to certain kinds of error and unintended bias. Quality control in the studies is also a concern, as I'll talk about a little more later. And we come up in this talk, and we think that it's possible to come up with qualitative conclusions, but there's a lot of conclusions that aren't possible to adequately address with the data that's available, and also qualitative conclusions -- there is not strong data on which to basis qualitative conclusions. And really what is lacking is well-designed, prospective longitudinal studies.

I will talk about one prospective study that was aborted early, and we put particular -- we find that that's

particularly convincing because of the study design, even though it was a small number of patients.

The sponsor talked in particular about the visual field Study 4020. This was an open-label study of field defect in complex partial seizures assessed by perimetry at regular intervals, enrolling 550 adults, 184 children. And the sponsor described the study arms.

Two study arms were previously treated with vigabatrin -- one remaining on vigabatrin during the study, and the other having stopped prior to entry. And then the other arm was patients not treated prior to or during the study. And only seven patients actually started vigabatrin during the study.

So while this is a large study, the types of patients that were enrolled were very problematic. And FDA finds that they don't represent an unbiased population. So the patients had been treated sometimes for

years, and almost all the patients who were ever on vigabatrin had been treated for a period of time before entering the study. And as I'll show in the next slide, we think that this may have biased the results, or biased the patient selection towards patients that did not have visual field defects or that had less-severe visual field defects.

Also, there's a concern in the enrollment that patients were selected because of fitting the expected pattern of a peripheral visual field defect. And so patients were excluded from this study if they had a central visual field defect. And the central visual field defect might have been attributed to glaucoma or to macular degeneration.

Maybe that was the correct attribution, but the FDA is concerned that maybe that was not the correct attribution. So those patients with central visual field loss were excluded from the study.

Also, there was a high dropout rate, which raises concern about the patients left at the end of the study not representing the whole patient population. In addition, FDA is concerned about poor quality of vision testing in the study.

This is a quote from a discussion at the Study 4020 steering committee, and it addresses the issue of bias. And this is the quote: "Current vigabatrin patients have already undergone visual field assessments." So that is they have been treated by physicians even for months or even years before enrollment in the study.

Since the vigabatrin is withdrawn in most cases where a typical visual field defect is diagnosed, as a consequence, nearly all patients remaining under vigabatrin have no visual field defect. And those were the patients that were enrolled in the Study 4020.

Regarding the quality of visual

field testing, this is also an excerpt from discussion at one of the Study 4020 steering committee meetings. And I quote, "As a general consideration, the experts stressed the difficulty to obtain perimetries of good quality. Only 10 percent Goldman and 50 to 60 percent super threshold and threshold perimetries are of good quality."

Regarding the dropout rate, again, there's first the problem of enrolling patients who have already been treated with vigabatrin. But even after that, there were 2,583 patients screened and only 735 patients enrolled. And they might not have even represented the population of patients screened. And then out of that 735, there were 524 that had even one visual field that was valuable.

And so it's hard to know how affected the patients who did not even have one valuable field -- how severely affected they might have been.

And then as far as the prospective nature, there wasn't much prospective data collected. So there was cross-sectional data on these 524 patients. But they weren't really followed very effectively. I think it was brought up in the last talk how it's possible to do serial testing on patients. And in this study, it didn't seem to be easy to accomplish that. There were 140 patients with two fields, 111 with three, and so forth. It dropped off with serial testing.

There are studies, again, already mentioned before, that we felt -- the FDA felt -- were more reliable than Study 4020. And I want to stress, and I think I'll stress later, that we don't necessarily think that these studies provide anything like a definitive answer about the visual field problems or central visual acuity problems, but we felt that these studies were more reliable than Study 4020.

And the first was Study ROO3. That

was the prospective study I just mentioned that was the study design that we would most trust. But that study only enrolled 25 patients. I'll still talk about that more.

The Pooled Cohort Study, we think importantly was a cross-section of a defined group of patients. So it was patients who were enrolled in open-label vigabatrin studies at the time. And we think that that better represents a population of patients than Study 4020, which it's hard to know actually what patients were enrolled in that study.

And then there's detailed case series and case reports. And this gets more to the point of central visual acuity problems, because fundamentally, the studies that were designed to look at the visual field defects did not look closely enough at the central visual acuity to provide adequate evidence that mild or moderate decreases in central visual acuity didn't occur. And in

the case series where patients were examined carefully, that gives us some indication at least of the outliers, or the potential maybe that would occur with visual acuity loss.

So first, to go to the question of the location of the defect in central visual acuity for peripheral visual field. And I think there's no doubt first that visual field defects -- peripheral defects -- do occur. And I'll describe that in more detail later.

Again, the visual acuity in the central retina has not been well-studied. But the published studies indicate that damage can occur. This study by Miller was already talked about, and essentially, it's the same data. There were a case series of complex partial seizure patients in a sponsor safety study. 32 patients on vigabatrin for a mean of about 4 years; 12 had apparently reduced visual acuity between 20/25 and 20/60.

A group of 10 matched patients all had normal acuity and normal color vision. And granted, this is a report in a publication but from what we can tell, this is -- it gives a reliable indication at least that visual acuity can be decreased in vigabatrin patients.

This is also taken from a publication by the Westall Group, which is very much involved with the infantile spasms safety testing. This particular patient is a 10-year-old girl with complex partial seizures. There's arrows -- it's a little hard to see -- but arrows indicating wrinkling in the macular.

And so there's evidence -- and there's no -- it was the author's intention, FDA thinks, to indicate that this wrinkling in the macular was at least likely associated with vigabatrin damage.

Similar kinds of wrinkling or pigment abnormalities have also been seen in

publications about adults, for example, Krauss (?) and Miller. FDA is concerned again that even though damage might be mild or moderate -- damage to acuity, that is -- that might be enough to impair function.

Since there's not very much known about the damage, too, there's a concern that the damage might be progressive either while still taking vigabatrin or even after stopping vigabatrin. And then there's also a concern for future additive damage. Maybe thought it was a loss of functional reserve, because diseases like macular degeneration or glaucoma are fairly common in the population.

And while we don't have data about this, there's the concern that patients who have some damage to central acuity or to the central retina will have a worse course from other diseases -- additive diseases, perhaps.

Next is the question of severity. And again, almost all the data that we have

is limited to the visual field constriction. I think that -- or FDA thinks that there's really no doubt that it's highly variable. The degree of visual field constriction occurring from vigabatrin is highly variable, ranging from mild to severe.

The dotted red line indicates a normal Goldman field. This is what could be considered a mild defect. Again, actually, I'd like to point out now that there's not really a well-defined correlate, shall we say, of mild, moderate, and severe. So different terms are used in different studies, and then what would really be the most desirable is some correlation with the patients' symptoms. And again, that data is really lacking.

But this kind of understanding that while I'm using the words, they're not well-described, actually.

The patient on the bottom is severely affected, with about a 10 degree

field from central acuity. And this patient also has a homonymous hemianopsia. And this illustrates the point that some patients with epilepsy will have other visual field problems, or visual problems again that causes an additive problem with their vision -- the visual ability.

Getting back to Study ROO3, this was the prospective study that was aborted. 25 subjects were enrolled out of a planned 200. The median cumulative dose of vigabatrin was 1,100 grams. Median duration of treatment was 500 days. And 7 patients out of the 25, about a third, developed a field defect. Six of seven of these patients developed a visual field defect shortly or after -- before or shortly after one year.

Four of seven of the defects were mild. One diagnosed -- a mild one diagnosed. And the definition that I'm using here -- and I'll explain a little bit more later -- is that's within 30 to 40 degrees of central

vision. And 3 of 7 defects were moderate when diagnosed, with moderate being defined as within 20 or 30 degrees of central vision.

The Pooled Cohort Study, which again was previously mentioned, that was a cross-section of patients in vigabatrin studies ongoing when the field defect was found. And certainly, this study has strengths and weaknesses, which I'll briefly describe.

Some strengths that FDA feels the study has is that it was a high proportion of a defined cohort of patients that were tested. 454 patients were tested. 64 were exposed for less than six months. There was an unexposed control group with a low false-positive rate for a visual field defect.

Weaknesses of the study include that field tests were done at a single time point; field test methodology was not standardized; the patients had different

baseline characteristics like age and they were from different countries. And very importantly, the study was conducted by the previous sponsor. We don't have very much data from the study. So it was documented for us in previous submissions, and also documented in the periodic safety update reports. Still, from these previous conclusions, we see that 22 percent of patients were found to have mild constriction; 31 percent moderate; and 27 percent severe.

Now, putting together the prospective Study ROO3 and the Pooled Cohort Study and published K series and trying to kind of come up with an overall conclusion, FDA thinks that we can say that by five years, roughly a third of patients are affected by visual field constriction, and in that one third, there's roughly an equal distribution. The way we see it, it's constriction to within 30 to 40 degrees of

central acuity, which is the -- I'll get it -- which is the blue line; moderate is within 20 to 30 degrees, which is the orange line; and severe is within 10 to 20 degrees -- the black line.

And then, of course, as I had mentioned, it's important to try to figure out what we mean by mild, moderate, and severe. What are the functional effects, or what is the disability for the patient? I think the first and very important thing to say is it's not really known. And FDA thinks that certainly, asymptomatic does not mean clinically insignificant.

Some patients are asymptomatic, but again, most are not. And it kind of goes to the nature of insidious loss of function, and that insidious loss of function can be asymptomatic. It can be difficult for patients to appreciate, even though it affects their lives, even though it affects their function. And this is definitely true

of visual loss.

Also, there were other patients who attributed what seems like symptoms of visual loss to other problems -- say, clumsiness or drowsiness.

FDA's estimate of disability from visual field defect -- from vigabatrin visual field defect -- and again, this is an estimate because it hasn't really been studied -- is that a mild defect would lead to inability to drive a car, for example; that moderate field defect would lead to bumping into objects, difficulty with ambulation, with walking, and clumsiness; and that severe defects would lead to difficulty with many daily activities, although it is important to note that with what we've seen is mostly not severely impaired central acuity -- most patients would remain able to do household chores, shopping, and necessary business.

Next is the question of

reversibility and stability of damage. And generally, it's accepted that the damage to the retina is essentially irreversible, with some rare reports of partial improvement.

The question of stability is more complicated, and it breaks down into two separate questions. There's a question of stability with continued vigabatrin use, and the second question is stability after stopping use of vigabatrin. With continued use, most of the data is cross-sectional, and fundamentally by that kind of design, that data can't address if vision continues to decline if there's continued vigabatrin use. And so to answer that question accurately, long-term visual field testing, repeated visual field testing, would be required.

There is some data -- going back to Study 4020 -- there is some longitudinal data in Study 4020 which suggests that visual field continues to progress if vigabatrin is continued. And this is from a small number

of patients from this large study, but in this small number of patients where this analysis could be done, 35 percent -- 12 out of 33 patients -- progressed while on vigabatrin, and 13, percent or 3 out of 17 were called progressors -- patients who had never taken vigabatrin.

And so while likely -- or perhaps the 13 percent that progressed who had never taken vigabatrin represent false-positives, the 35 percent who took vigabatrin is much larger than the 13 percent. And it certainly qualitatively at least suggests that there's progression with continued use of vigabatrin.

Even with continued use -- even with continued use for many years -- there's not much evidence that the field defects progress to closer than 10 degrees of central vision. But FDA is still concerned about diagnostic bias for these patients who might have loss of central acuity or constriction to within 10 degrees, because as I had noted

for Study 4020, patients on vigabatrin can also be diagnosed with glaucoma or macular degeneration. And even as I speak sometimes about it and a lot of people speak about it, we talk about the peripheral visual field defects from vigabatrin.

And we think it is possible that there's diagnostic bias -- that patients on vigabatrin who might have had loss of central vision from vigabatrin were diagnosed with some other disease.

And this is just a post-marketing report that we think shows this possibility. A 60-year-old man taking vigabatrin 2 grams per day for five years developed what was called senile macular degeneration. Other findings included abnormal color vision and bilateral visual field constriction. And we don't know what was the cause of this patient's problem. But there, again, is possibly a tendency to call something age-related or senile macular degeneration

instead of diagnosing it as related to vigabatrin.

And the next question is progression after stopping vigabatrin. And it certainly seems that any progression, or even slow progression, if it would occur after stopping vigabatrin, would greatly increase the risk, because of course, it would happen over many, many years.

This is the kind of data that's available for trying to answer that question. And it was brought up in discussion the approach of averaging change or taking a look at individual patients. In the data that FDA has for taking a look at individual patients shows that some get much worse -- this is just two tests. It's not serial testing, but there isn't hardly any serial testing available.

But this shows that some patients get much worse. Some patients get much better. Some patients stay the same. And so

first averaging the patients together doesn't really answer the question.

But I think fundamentally, because of the test to retest noise in visual field testing, this is a very difficult question to answer. You would need to carefully examine visual field tests -- many visual field tests over a long period of time to address the question with any precision at all. And FDA is not aware of any data to support a conclusion either way.

So what FDA thinks can be said is that in most patients vision doesn't rapidly deteriorate after stopping vigabatrin. But again, what I showed on the previous slide, there's other cases of apparent progression.

Next is the question of time to onset and speed of progression. So again, cross-sectional studies -- the available studies by design are poorly designed to address time to onset and speed of progression. Particularly with Study 4020,

many patients were treated for years before entering into the study. So if a patient had been treated for four years before entering into the study, the time of onset wasn't four years. The visual field defect occurred at some time before that, but you really don't know when, because you weren't monitoring the patient then. And again, prospective longitudinal data would be needed to answer that question.

An important distinction to make, which I'll get to later, but very important distinction to make, is between time to onset versus speed of progression. These are just idealized diagrams of what might be occurring. Vision decreases over time, and at some point, there's detection of the visual field defect. In both of these, the detection occurs at the same time point. And so this could be defined as time to onset. But it's very different from speed of progression.

On the left, it's a slow speed of progression, and on the right, it's a rapid speed of progression. And unless you can accurately follow patients along the way, you don't know when you detect the problem -- if it happened slowly over time or possibly the patient was on vigabatrin for a number of months or a number of years and the visual field defect could have developed relatively rapidly. Again, you don't know how rapidly.

We have some evidence to address this question. Again, going back to the prospective Study ROO3, there were 25 subjects. Seven patients, or 28 percent, developed field defect. One patient developed a field defect after about two months of treatment, and five developed a field defect before or shortly after one year.

Now, the severity of the defects when diagnosed helps to address the question of speed of progression. So visual field

testing was conducted every three months. Three of seven defects were not defected until moderate severity. So the question is why did that happen? Why weren't those patients detected when they had mild defects?

Why were they only detected when they had moderate defects? And the ultimate answer is that we really don't know. But certainly one possibility is that they were monitored every three months and that they didn't have a defect, and then between tests, they developed, instead of a mild defect between the three-month tests, they developed a rapidly developing defect to moderate severity.

The Pooled Cohort Study is a cross-sectional study of patients on vigabatrin. And as a cross-sectional study, it wasn't designed for determining speed of progression or time to onset. And the previous sponsor, though, had modeled the incidence of visual field loss. And again,

this makes some assumptions, but we put some credence on the findings of the previous sponsor.

And there's some assumptions made about if you have a visual field defect one year, maybe it's reasonable to assume for the sake of the model that the visual field defect truly appeared at half that length of time. You detected it one year; maybe it appeared at half a year. So based on those assumptions, the peak incidence of visual field defect was at about one year.

And there was with continued use an accumulation -- a slower accumulation -- with time of patients with new visual field defects, and the overall prevalence of defects increasing to 30 or 40 percent after five or more years.

So FDA's conclusions from this data -- which albeit is not perfect -- is that the visual field defect is detected at less than two months in some patients. And

again, detected -- it doesn't really mean when the damage first started to occur. And if it was detected when it was still clinically insignificant, this number less than two months doesn't really address that point. And peak incidence is at about one year.

Next, I'll talk about dose and time effects. This study is a cross-sectional study of patients who had been treated for -- this is out of the literature -- of patients who had been treated for various lengths of time -- one year up to 14 years. And it shows the degree of visual field defect. And this study didn't show a relationship between exposure and the likelihood or the severity of having a visual field defect.

And the same results were found for the maximum daily dose. While this study was negative, some studies have shown a weak relationship of both duration and dose.

But the conclusion that FDA comes to regarding dose and length of exposure is that there's a high risk -- we're not entirely sure what it is -- even with short use. And we're not entirely sure how short that use is. And that there's a high risk even with lower dose, or certainly with the doses that have been used for epilepsy.

Then there's a question of monitoring prevention. In adults and older children, direct testing of the visual field is certainly the most direct way to address visual field constriction. Direct testing of acuity also is the most direct way of addressing that question. And I won't talk too much about acuity, but as the sponsor had mentioned, testing of acuity is not entirely straightforward. Cataracts have to be accounted for. Refraction has to be accounted for.

And that's part of the reason that FDA believes that it's not established what

effect vigabatrin has on central visual acuity.

In young children and patients that can't perform subjective visual tests, electroretinography has most often been used, and that's what FDA has data about. We have very little data -- almost no data -- about other methods. And so we're concerned that while many methods might be mentioned, we are not sure that they actually can detect the visual field defects or the damage that vigabatrin causes. There just isn't data, for example, or not much data that can tell us how successful OCT is. While it's promising, there isn't much data saying that it can be useful for detecting the damage.

And of course, it's critical to draw the distinction between preventing damage and detecting damage. And those are really two different things.

It's much harder to prevent the damage than it is to detect damage that has

already occurred.

This is a quote from a publication from Dr. Wild about perimetry -- about visual field testing. "The results of perimetry can often be inconclusive and frequently require one or more confirmatory examinations, even though the results of the subsequent tests can remain equivocal." And it's already been talked about today that perimetry is a subjective technique, and that perhaps 20 percent of patients -- of vigabatrin patients -- would not be monitorable by perimetry.

FDA believes that there's actually an intermediate range. There's patients, perhaps 20 percent, that can't be monitored. But then there's a whole range of patient abilities, and it's difficult to know how successful patients will be at perimetry. Perimetry is subjective. It demands concentration and attention, particularly difficult with patients with any degree of

cognitive impairment.

It's a learned skill. And that's an important point for trying to prevent damage. The first several tests are often unreliable. So that makes it difficult to establish a baseline before treatment is started. Also, the field -- the actual size of the field is expected to get bigger over several tests as the patient's skill increases. So at the same time that the physician is trying to detect a decrease in the field, an increase in the field is occurring because the patient is learning how to do perimetry better. And this might very well confound early diagnosis.

Now, when FDA tries to consider a test -- a clinical test -- for preventing data, we think of a prevention window -- how or when can you find a problem to prevent a worse problem. Also, there's questions of sensitivity and specificity, and related to that is what test frequency would you need to

get what kind of result. And again, this is an idealized version of vision decreasing over time due to vigabatrin -- and the yellow points are field results which attempt to represent true vision.

So certainly, for patients that can reliably perform perimetry and that have a linear progression of damage, it's likely that early damage can be detected. But the question is how many patients are reliable test takers, and also very importantly, how many patients have slow linear progression. And as I mentioned before, we don't know what the speed of progression is.

So again, this is largely a hypothetical case, but again supported by some data, that the actual progression might look more like this, where at some point, there's tests that are normal, and then as in Study ROO3, the next three-month test shows that moderate damage has already occurred. And this would be in a patient who was a

reliable test taker.

So for this patient, perhaps, there's less benefit of testing. Damage occurs, but perhaps there's some benefit of testing, and the drug could be stopped before damage is worse.

For a lot of patients -- again, this is not necessarily just the 20 percent who might not be able to be monitored at all -- but for a lot of patients, the first few tests are uninterpretable. And later tests have a variable amount of noise depending on the patient. And so for these patients, after the damage gets to a certain degree of severity, it's likely to be detected. But it isn't really going to be prevented; it's just going to be detected and it's irreversible damage.

So while the patient gets correctly diagnosed, there really isn't benefit or preventive benefit of testing for a patient like that.

For patients that can't perform perimetry, the only method that we really have data about is electroretinography. And the sponsor, I think, too, thinks that that's currently the most sensitive and specific index of retinal injury underlying vigabatrin visual field defects. While we don't have a lot of data about the correlation of ERG with visual field defects, we do have some.

And going back to Study ROO3, zero of four patients with mild damage -- I didn't mention before these patients also had ERG -- and zero of four patients with mild damage by perimetry were detected by ERG, and only one of three patients with moderate damage by perimetry was detected by ERG.

This is a 10-year-old girl with complex partial seizures who was reported by the Toronto Group, which again we'll talk more about their data tomorrow -- they've done a lot of work with infantile spasms -- but this patient had severe field

constriction. This, again, is normal on the outside. The red is normal, and the black line is the patient's visual field. And this patient had a normal 30 Hz ERG. Anyway, so our conclusion is that while there isn't a lot of data, the data that we do have suggests that the sensitivity of ERG for visual field constriction might be poor.

So the conclusions -- the FDA conclusions -- are that vigabatrin causes visual field constriction; the onset and progression is variable and unpredictable for any given patient; a third or more of patients are affected after several years; and in about equal proportion mild, moderate, and severely.

Damage to central vision probably occurs in some patients, but there's very little data on the severity of the frequency of damage. Progression or progressive damage after stopping vigabatrin hasn't been adequately studied, but it's certainly

potentially of large clinical consequence for patients.

Visual disability occurs, but it's largely unstudied. And even in patients that fail to spontaneously recognize vision loss, disability -- visual disability can be present. The peak incidence of visual damage appears to be at about one year. Onset at a few weeks or months is not rare, although it hasn't been well-quantified. There's potentially a weak time and dose dependence, but FDA is not aware of safe exposure in terms of time or dose.

And FDA is unaware of how to adequately monitor for this adverse event. We don't know how to reliably prevent damage and also, we're unable to propose a sound monitoring plan based on the data that we have.

Thank you.

DR. GOLDSTEIN: Thank you.

Dr. Weaver.

DR. WEAVER: Hi. I'm Joyce Weaver, and I'm with the Office of Surveillance and Epidemiology at the FDA.

A risk evaluation and mitigation strategy is a risk management plan that uses strategies beyond routine labeling, to ensure that the benefits of a drug outweigh its risks. A REMS is designed to meet specific goals and mitigating product risks. The Food and Drug Administration Amendments Act of 2007 gives the FDA the authority to require a REMS.

A REMS can include these elements. A REMS can include a medical guide for patients. A medication guide is FDA-approved patient labeling that explains the product risks. There was a question about patient-friendly language, and it's to be geared at reading levels of sixth to eighth grade, or no greater than that. A REMS can also include a communication plan for health care professionals.

This might include, for example, a letter to likely prescribers that discusses the product risks. A REMS can include safety measures that the statute calls elements to assure safe use.

Elements to assure safe use can include training or certification of physicians who prescribe the drug or pharmacists who dispense the drug, for example, if extra training is needed. The health care professional might complete a training module, and then sign an attestation that they've received the training and that they understand the risk mitigation protocol needed to use the drug.

Another example of an element to assure safe use might be a requirement that the drug be administered in certain health care settings. For example, if a drug had QT prolonging effects, there may be a requirement that therapy be initiated in a hospital so that EKG monitoring could be

conducted, and so that emergency staff would be available should a life-threatening arrhythmia occur.

Elements to assure safe use can include documentation of following a safe use protocol prior to dispensing. For some teratogenic drugs, this might entail an attestation of contraceptive use and pregnancy testing for females of child-bearing potential, for example.

There can be required monitoring of patients. An example of this element is monthly liver testing for patients who receive a hepatic toxic drug. And finally, patients might be enrolled in a registry that follows patients receiving the drug. The registry can be used to follow the safety protocols needed and to collect data on drug-related injury.

So when should a REMS be considered? The statute states that products should be considered for REMS, if needed, to

ensure that the benefits of the drug outweigh the risks. The statute also lays out whether the Agency should institute a REMS. The statute states that we should consider the estimated size of the population likely to use the drug, the seriousness of the disease or condition that's being treated, the expected benefit, the expected duration of treatment with the drug, the seriousness of the adverse events that might be related to drug exposure, and the background incidence of those events, and whether the drug is a new molecular entity.

So by statute, these are the items that the agency must consider before instituting a REMS.

However, what we're asking the Committee to do here today is actually take a step back and consider something more basic today, and that is whether the risks of vigabatrin can be mitigated. The sponsor has proposed a REMS for vigabatrin, and they did

a good job of summarizing it. The goals have already been stated. You notice that the goals here all relate to the risk of the visual field defect. There are no goals that address the intramyelinic edema.

The REMS elements that are proposed by the sponsor -- as they stated before, they propose a medication guide. They propose a communication plan to communicate the risk messages. They propose elements to assure safe use, including that the initial prescription be by a board-certified neurologist; that there be prescriber education and attestation of an understanding of risk and the safety monitoring protocol. The physician commits to periodic visual field testing and attests to reviewing the medication guide with the patient.

And they propose distribution by a specialty pharmacy. Specialty pharmacies are sometimes used in risk management programs to perform some of the monitoring functions; to

enforce safety protocols; and to collect safety-related data on the drug, as well as to provide for controlled distribution of the drug.

The patients would be enrolled in the REMS registry by an enrolled prescriber. After receiving vigabatrin for a short period of time, the patients' response would be formally assessed. For infantile spasms, it would be after 2 to 4 weeks, and for complex partial seizures it would be after 12 weeks.

If the response is acceptable, the prescriber attests that the benefits of the product exceed the risks and the therapy would continue. As was noted by one of the Committee members, that's -- it's really looking at the benefits, because at that point, the risks to the individual patient are theoretical.

The visual testing is conducted on a periodic basis throughout the time that the patient receives the drug, and that periodic

visual testing as described by the sponsor would be mandatory for adults receiving it for complex partial seizures. The sponsor proposed an evaluation plan, and it's evaluated with surveys of the patients and the prescribers, data that's collected from the specialty pharmacy, compliance with the program elements, the safety protocols, and finally, adverse events that are reported for vigabatrin would be included in the evaluation.

The REMS proposal makes some assumptions that we're not sure are supported. First, the REMS assumes that the patients are not likely to lose vision during the initial period of treatment -- that is from the time that therapy is initiated through the time that the response to therapy is assessed, and until the time that the first visual monitoring on vigabatrin is done. And we're not convinced that this period of exposure is safe.

The REMS assumes that periodic monitoring of vision will preserve vision. And we think that some patients might lose clinically meaningful vision despite the periodic monitoring. And finally, the risk of intramyelinic edema is not mitigated by the REMS, in that there's no formal monitoring for it, although there is information about intramyelinic edema that's included in the REMS materials.

So to mitigate the risk to vision with periodic testing, we need to consider whether there's a safe period of exposure, or whether significant loss of vision might occur before detected with periodic testing, and whether it's possible to design a rational monitoring program to prevent loss of vision.

Can visual testing detect damage to vision reliable before the damage is severe? Do abnormal testing results need to be confirmed with repeat testing? And if so,

what additional damage might occur between tests? Do we know the significance of the intramyelinic edema? And does monitoring for this risk need to be incorporated into the REMS? And if so, what would that monitoring entail?

So the REMS issue for the Committee, and this issue has been incorporated in the set of questions that you'll be asked to consider, is whether safety monitoring protocols can be designed that will mitigate the risks of the visual defect and intramyelinic edema. And if so, what monitoring protocols should be implemented? What protocols for children and what protocols for adults?

DR. GOLDSTEIN: Thank you. So what I'd like to do now is have some time for clarifying questions, first for the FDA, because hopefully we'll have time afterwards. We can then go back to questions for the sponsor, and I believe the sponsor had one point that they

wanted to make also in response to a question that we ended with at that session.

But first, qualifying questions for the FDA. And if I might, I just have one question I'd like to make sure about. The sponsor presented data on a retrospective review of MR in which they said that there was no difference in the appearance of MR lesions. In the FDA presentation, that study wasn't addressed. Does the FDA believe that there is no difference, or that there is a difference, and they disagree with that conclusion from that study?

DR. KATZ: Dr. Sheridan reviewed that in detail, and I think he was going to talk about it tomorrow in the context of the pediatric, although it's all adult data. And I think we generally agree that there didn't seem to be a signal in adults that was referable to intramyelinic edema on MRI.

I think we're mostly in agreement.

DR. GOLDSTEIN: Thank you.

Dr. Kramer.

DR. KRAMER: Two questions about the REMS. The sponsor seemed to refer to a patient agreement. And I didn't see that mentioned on your slides.

Could you clarify whether there is a required patient agreement?

DR. WEAVER: That is included in the proposal, yes.

DR. KRAMER: And then the second question is, in terms of the regulatory requirements for REMS, the FDA is focusing on identifying something that would actually prevent worsening -- identifying something that could prevent further worsening. Is it also consistent that you could assess benefit exceeding risk if -- even if the worse case scenario, you couldn't prevent it; you could only identify it -- if patients were desperate enough to be willing to accept that reality -- the worse case scenario?

So everything is being posed in

terms of can we mitigate it, but is it consistent with the legislation that a REMS program could just as early as possible identify for the patients' choice, but that they could still make the decision to seek the effectiveness?

DR. WEAVER: Yes. You know, I think that we certainly feel more comfortable if there's a risk that we can actually mitigate. But it would be possible for an important drug to have informed consent with an understanding that we might not be able to fully mitigate it.

DR. GOLDSTEIN: Thank you.

Dr. Sleath.

DR. SLEATH: Dr. Weaver, I had a couple of questions about the REMS as well. One was, the sponsor had a lot of detail about training of physicians but not pharmacists. And I just wondered, are specialty pharmacists or pharmacies automatically trained?

And the second question has to do with children. When children hit a certain

age, usually you have materials for them and their parents and consent forms for both, and in the sponsor's materials, I didn't see anything about that. They were kind of lumped together. So I just wondered the FDA's kind of rules on that.

DR. WEAVER: You're talking about possibly patient ascent at a certain age?

DR. SLEATH: Ascent, as well as the -- you know, the surveys. Much research in pediatrics -- I do work in asthma -- shows that parents and children often don't agree about -- you know, their level of -- you know, impediment by the disease -- that kind of thing. So I just wondered, both with ascent and also with the monitoring and the questionnaires that are asked.

DR. WEAVER: So far, I think that it's focused more on parents and guardians, but that's a good point to be made. In terms of the specialty pharmacies, the training actually would be part of the contract between the

sponsor and the specialty pharmacies. Certainly, specialty pharmacists or pharmacists who work in specialty pharmacies don't automatically know this information, so there would need to be training material for those pharmacists.

And the way that they conduct their business is part of the contract.

DR. GOLDSTEIN: Dr. Nelson.

DR. NELSON: I actually have a question for Dr. Weaver and one for Dr. Farkas, as well.

In the REMS, one of the things that doesn't appear to be listed -- and perhaps it doesn't belong there -- is some of the details about how the risk/benefit assessment is done. The one thing I guess is unclear to me is how will it be assessed that somebody has failed an appropriate number of anti-epileptic drugs before they're put onto this new drug? I know that the indication was -- you have to fail two monotherapies and

one combination therapy, but it didn't specify anything about what those drugs were, exactly what failure is, and then in fact, it actually has to be performed in order to get onto this medication.

DR. WEAVER: You know, I think I would let the sponsor respond to some of their own thinking on their proposal, but I would think that what they're doing with putting the requirement for the board-certified neurologist would kind of take the place of that -- that we wouldn't be necessarily going after and checking whether the board-certified neurologist had checked off -- you know, all those items. Although we could. That's a possibility that we could.

DR. NELSON: I mean, it would just seem like that would be an important thing to look at since that's what we're basing our indication on.

And for Dr. Farkas, if I can, my understanding of the different tests that

we've already discussed for assessing the development of the peripheral field defect is one of the tests is a clinical or a functional test which is -- you know, the perimeter -- the perimetry testing. One of them is a physiological test, I guess -- you know, the retinograms and the other one is, I guess, more of an anatomical test -- the OCT.

DR. FARKAS: That's correct.

DR. NELSON: Would there be -- is it conceivable that if you put those three tests in a series, you'd pick up more patients than by looking at any one of them individually? And would there be a role for doing something like that rather than saying a negative test is a negative test? Because they're all quite different, as I understand it.

DR. FARKAS: Right. I think that's certainly a possibility. It just hasn't been explored.

DR. GOLDSTEIN: Two excellent questions. And this afternoon in our

discussions, we luckily have a pediatric ophthalmologist, as well as a pediatric epileptologist. And I think both those questions are things that we're going to be discussing in detail.

Dr. Temple, you had a question.

DR. TEMPLE: Yes, I wanted to ask Joyce, have we ever actually had a REMS that limited use to people with particular board certification? I think even for Tysabri, where we're very nervous about who's using it, I think we say you have to have appropriate training, you have to say that you understand these things. We haven't literally done board certification, I think. So I wondered.

Have we actually done that?

DR. WEAVER: No, we have not. You're correct. We've focused more on the body of knowledge that the prescriber would need instead of the training of the physician up to the point of prescribing. And one of the reasons that we have shied away from that is that we do worry

about patients in underserved areas. So to this date we've not done that.

DR. TEMPLE: All right. So we do have some historical reluctance to do that.

DR. WEAVER: That's correct.

DR. TEMPLE: The other question is, or I guess sort of a comment, we don't usually ask for consent in these documents. What we ask people to say is that they've been informed -- that they've read the materials and stuff like that. Consent in a setting where anybody can refuse therapy -- you know, you can't make a person take the doctor's recommendation. So consent is a slightly funny term there, and we usually have them assert that they've been informed of these things which is somewhat different.

DR. WEAVER: Right. They say they understand and they make commitments. But, yes.

DR. TEMPLE: Yes. And they make promises and all that. Right. Okay.

DR. GOLDSTEIN: Dr. Jung.

DR. JUNG: I have three questions. The first is for Dr. Silber regarding the issue around MRI scan changes on the patients who received this drug. You mentioned in your presentation that you thought that the MRI (inaudible) I guess it's not clear to me how the sponsor (inaudible).

DR. SILBER: So specifically, that analysis was undertaken with a broader definition of MRI abnormalities intended to capture the largest number of abnormalities both for vigabatrin-treated and vigabatrin-naïve. What I was referring to in terms of pattern was that the pattern observed for those that were detected, that were not different between vigabatrin-treated and vigabatrin-naïve, actually were in hemispheric locations as opposed to deep structures where the findings existed preclinically.

DR. JUNG: So going back to Dr. Katz's comments, does that mean that the FDA is comfortable in terms of its initial concerns

with IME?

DR. KATZ: I think largely, we don't know if there are any clinical consequences referable to IME and whether or not it's even occurring in adults, let's say. I think we look to the MRI data to try to get a handle on that and I don't think we thought there was a signal from that. So I guess we're not aware of any particular clinical toxicity referable to the IME I guess is the best way I'd put it.

DR. JUNG: And then my second question is to Dr. Sergott, around the OCT, do we currently have data regarding OCT studies in the patients who have been studied or have been exposed?

DR. SERGOTT: Yes, we do. We have a paper that appeared in Investigative Ophthalmology and Visual Science that we should have several slides here to describe. It's from Dr. Wild's group in Wales. And Vander (?) took a study of cross-sectional data -- not longitudinal data -- and again, I think they're

looking for the same thing that we're all struggling with. That is, what is the signal and are there other ways that we can do this?

So 13 patients had field loss with vigabatrin in Group 1. Eight patients had vigabatrin therapy in normal fields; 2 groups were on other agents; and 20 normal patients. Perimetry was also done. And here's their data. The patients on vigabatrin with field loss are represented by the closed and shaded triangles. The open circles represent patients on vigabatrin without visual field loss. And on the X axis is duration of therapy, and the Y axis is retinal nerve fiber layer thickness.

For those of you not familiar with OCT, the test takes about a minute, is painless, non-contact, non-invasive. Best measurements are done with dilated pupils. The patients simply look straight ahead and a technician centers a circle of light around the optic nerve. And then very advanced

algorithms and interferometry are used to get a measurement of the thickness. And variability can occur in this test because of the way that light is centered. Newer machines have a better form of what's called registration. And what we can see here is that the thickness of the neurofiber layer in microns was lower in those patients who had visual field loss.

The normal should be somewhere about 100 microns of thickness. That's the mean. That's the average of 12 30-degree scepters around the optic nerve. And then these investigators also looked at the same thing looking at cumulative dose, and again those patients on vigabatrin also had loss in this area.

DR. GOLDSTEIN: Thank you.

Dr. Rizzo.

DR. RIZZO: Thank you.

DR. SERGOTT: So in summary then, there is some cross-sectional data here. What's

also interesting is that we can look at the macular thickness. And very accurately. This is a wonderful technology for looking at disease of the vitreomacular interface. So they saw no abnormalities of macular wrinkling, and they saw no thinning of the macular, which is usually in other diseases been associated with central loss of acuity.

DR. GOLDSTEIN: Thanks.

Dr. Rizzo.

DR. RIZZO: Yes. I wanted to know if a MRI scan is capable of ruling out intramyelinic edema. And if so, what are the sensitivities and specificities of the techniques used? There are MRIs and there are MRIs. Were they T1, T2, gradient echo diffusion weighted images? I think that's important to consider.

And I have a follow-up question on that.

DR. GOLDSTEIN: To comment on MRI technology and the sensitivity associated with

it, I'd like to call on Dr. James Wheless to comment.

Dr. Wheless.

DR. WHELESS: I'm Jim Wheless, from the University of Tennessee.

The MRI scans in the modern era -- most are done in 1.5, some with three (inaudible) machines, but with standard sequences using epilepsy patients, T1, T2, and flare sequences have really been pretty standard for at least probably a decade now. In the last few years diffusion weighted imaging have been added to that. So I think most neuroradiologists would feel pretty comfortable with standard scans knowing that the T2, the fare, that those were there -- that if there was significant intramyelinic edema, that that would show up.

DR. RIZZO: So we actually know that though? You know, we have examples of patients with traumatic brain injury who have illusions and they don't show up on standard MRIs, but use

different techniques, and lo and behold, they show up. You can make similar arguments about stroke. It shows up on diffusion weighted imaging.

You know, where the MRI is done -- you know, when they're sensitive enough to pick up these lesions that we've never actually seen before with clinical tests.

DR. WHELESS: You might even go back -- I'm not a radiologist, obviously. You might go back even to the FDA, but my understanding is that when this lesion was first discovered in animals, MRIs were done in those animals where you could histopathologically verify lesion with the MRI. It was found to be sensitive, and that's what led to in the late '80s and '90s, MRI being used in the complex partial seizure protocols as a surrogate biological marker for that in humans, because it was felt to be specific based on the animal data where you had histopathology.

Rusty may want to comment.

DR. KATZ: Right. No, just to reiterate -- right. We had imposed this requirement when we put the studies on hold in the '80s for the sponsor to develop a validated way to pick up a lesion early when it might still be reversible, and I think we think we were convinced that in the dog the MRI was sensitive to the very early -- the onset of the very early lesions. So we thought that was a validated way. Whether or not that translates into humans, we don't know for a fact. But we believe it was validated in the dog.

DR. GOLDSTEIN: Right. And again, you stipulated that -- you were satisfied with the comparative study technologically that it's adequate and you thought -- you agree that there's no difference between the treated and the untreated patients.

DR. KATZ: Right.

DR. WHELESS: The reason that I ask is because whenever there is bilateral visual

loss -- of course it's important to consider bilateral retinal and optical nerve illusions, but another important cause is lesions in the central visual pathways in the occipital lobe -- examples where you might not see structural or MRI changes in the occipital lobe but you would have bilateral visual loss -- would include things like visual variant of Alzheimer's Disease, corticobasal degeneration. So it happens.

DR. GOLDSTEIN: Thank you.

Dr. van Belle.

DR. van BELLE: I still had a question for the FDA. Is that appropriate to ask?

DR. GOLDSTEIN: Yes, please.

DR. van BELLE: I have a question for Dr. Farkas. In your slide 47, you talk about that there's a high risk of visual field defects over the range of doses available. I'd like to know what you mean by high risk. Can you give me a number? Is that 30 percent? Is that 60 percent? What range are you talking about?

Secondly, is the high risk potential or is it demonstrated? If it's demonstrated, what is the evidence for that?

DR. FARKAS: Well, I think that maybe if you could show slide 46. So again, this is --

DR. van BELLE: I mentioned slide 47.

DR. FARKAS: Right, but the conclusions on slide 47 were based on part on data on slide 46.

DR. van BELLE: Thank you.

DR. FARKAS: So I think the answer to the first is that we're not really sure if high risk means 30 percent or 60 percent. But in that range we would consider that high risk. We're uncertain of the number.

And I think the other question as about dose. And the bottom part of that slide shows 1,000 mgs daily dosing. And certainly, visual field defects occur at that dose. There's fewer patients in the 1,000 mgs there. So it might look like there's

more severe or more field defects at 2,000, but they're actually fairly similar. So there isn't really on that data any discernable effect of daily dose or again on top of duration of treatment. So actually, there's some serious discussion still of whether this could truly be called an idiosyncratic adverse event. So it might not be related particularly to dose or time of exposure.

DR. van BELLE: Thank you.

DR. GOLDSTEIN: Dr. Vega.

DR. VEGA: My question was for Dr. Weaver, and it's regarding one of the REMS elements is the medication guide for patients. It's been my experience with the type of patients that I see that 99 percent of them often don't understand dose guides. And often, the enforcement at the sixth grade level is really not done. They are often very complex. I have -- I mean, a lot of the patients cannot even read so we have to use other means of

communicating to them the risk/benefits of what we are trying to say. Also, we have a lot of patients who will let us think that they understand, when in fact they are very confused about what we are telling them.

So are there any more specifics in terms of how that's going to be worked out?

DR. WEAVER: So you're talking -- I hear two things in what you're saying. One is that you're not quite buying that our medication guides are at a sixth to eighth grade level. And the second thing is that you're pointing out that there are problems with literacy that show that perhaps there are patients who function at less than that and need materials. I don't think I have a good answer for you but I acknowledge what you're saying.

DR. VEGA: Yes. It's not only literacy but it's now literacy is -- it's complex. In terms of communication, it's a complex situation.

DR. GOLDSTEIN: Thanks.

Dr. Gorman.

DR. GORMAN: My question is for Dr. Farkas. We've raised some issues about the weakness of the time and dose relationship. You proposed several potentially catastrophic short-term effects. One of the strengths of the passive drug adverse event reporting system we have is paying up rapid sudden adverse events that are unusual -- 1.5 million exposures, people exposure over Europe and the rest of the world.

Have there been any reports -- because I was unable to find them -- of sudden loss of vision, sudden loss of color vision, or complete loss of visual fields? Because those would be the kinds of things that case report physicians would be likely to report. And especially, I looked at the time after the first reports of the visual field loss was coming out when you'd expect physicians who were treating these patients to be sensitized to visual field

loss and report them.

DR. FARKAS: Well, I think that there's two questions there. One is the speed of vision loss -- the speed of the more ordinary visual field constriction. And I'm not sure that post-marketing reports can capture how suddenly that occurred. The patient, I think, oftentimes is not detected and then is detected. And in a scenario like that it's very difficult to know if the damage was occurring slowly over time or if it occurred -- anyway, I don't know if it's overnight but in a month or two, it's hard to know.

The second question about central acuity loss is that we do think that it's certainly not common. That at most, it could be rare. And we don't know that it occurs, but what's disturbing is that patients with -- patients who are on vigabatrin do suffer central acuity loss. But they're not diagnosed or that's not diagnosed necessarily as due to vigabatrin. So while you're

correct in saying that there are very few patients to point to who lost central acuity attributed to vigabatrin, there are patients to point to who lost central visual acuity. Say, patients who are on vigabatrin and lost central visual acuity attributed to glaucoma, which of course is another optic neuropathy, which could have similar signs to vigabatrin toxicity.

DR. GOLDSTEIN: Thanks.

Dr. Lu.

DR. LU: Yes, I have several questions following around that comment. For one thing, you mentioned that there will be a confirmatory test for the cases. I mean, is that the same method or do they have to have lapsed certain time? Or you can immediately follow a positive test assuming that's trying to exclude false-positives?

DR. FAUGHT: The recommendation of the Royal College of Ophthalmologists is quite specific that a confirmatory test should be

performed within one month. We, in our labeling, we're not specific about the exact time recognizing difficulties of getting to see an ophthalmologist at times, so we didn't want to put too tight a restriction on that, but we said in a timely fashion. And that should increase the frequency of monitoring at that point to a frequency of every three months. So that was the way we dealt with that.

DR. LU: What is reliability on a same day test? Was there any test --

DR. FAUGHT: On the same day --

DR. LU: Yes.

DR. FAUGHT: On the same day test? Perhaps I could ask Dr. Sergott, who is a neuro-ophthalmologist, to comment on the test-retest reliability.

DR. SERGOTT: Yes. So coefficients of variability have been studied with visual fields. And as I mentioned earlier, they really depend upon how much instruction the patient is given, age, other concomitant ophthalmic

diseases.

For your specific question for that specific patient and the scenario that Dr. Sagar talked about, we have a patient who comes back, feels unreliable. Now we're dealing with a tertiary care center, neurologists, neuro-ophthalmologists. And that patient is going to get back and reassessed quickly.

Coefficients of variability are also dependent on severity of loss. So it can range from anywhere from 0.6 to 0.95 depending upon the testing circumstance, and as Dr. Farkas mentioned, the repeat testing. Patients do get better with this test as time goes along. So the short answer is it has to be considered, but in the real world we would put all of this together with the rest of the patient's data. Again, if they can't do a good static field we would do the Goldman.

DR. LU: Yeah, I'm not sure if I get the answer. So let's say for the mild patients.

DR. SERGOTT: Yeah. In the mild patients, our concern, just like with glaucoma, we can't always detect mild glaucoma with fields. The 30-2 perimetry test actually was developed because 90 percent of glaucoma patients will start in the central field. But 10 percent are out on the periphery. So as a clinician, if we think this patient has glaucoma, we still have to look at the peripheral field.

So it is, again, a process; not a single event. And I think that with this monitoring program and with the -- you know, input from the agency, this will be the drug that has potential visual side effects that will be most carefully studied and the patients will be most carefully followed.

DR. GOLDSTEIN: Thank you.

DR. LU: Can I follow, sir?

DR. GOLDSTEIN: Sure.

DR. LU: Sorry. So for ROO3 study that you have rigorous like every three-month

follow up time, and when you mentioned there are three like equal distributions of severity, there was the first capture before there was a normal one, then you get either severe or moderate VFD?

DR. SERGOTT: In those 25 patients, there were no severe, but there were -- I believe it was three that were captured when they were moderate. And I think four when they were mild.

DR. LU: Moderate. Okay. And so for the curve of -- for the slide 43 in your presentation about distribution, I assume that was based on the 4020 study, and that's for mild and all the cases?

DR. SERGOTT: This is the cohort study.

DR. LU: Oh, that's the cohort study.

DR. SERGOTT: This is a different study than 4020.

DR. LU: That's including mild and --

DR. SERGOTT: Excuse me. This was

including all different severities.

DR. LU: Okay.

DR. SERGOTT: I didn't explain this, but this was combining patients with all different severities just trying to estimate when the field defect would have been discovered if it had been a longitudinal study. So there were some assumptions in that.

DR. LU: And do we know -- I mean, for the -- because the sponsor mentioned there are other drugs that have been approved with the VFD side effects. Do we always have a good understanding of their timeline and the progress and reversibility?

DR. CHAMBERS: This is Wiley Chambers. The variability of what we know on different products that have visual defects varies tremendously. And they have all been evaluated on an individual basis. There are some that we don't have the advantage of having 10 years of experience on and have just what's in the clinical trials. We have tended to be -- have

more stricter warnings on those particular things and have been more restrictive in the population and others where we have just listed it as potential adverse events. So we have a full range.

DR. GOLDSTEIN: Thank you. We have about five minutes and five more folks from the Committee with questions. So this should work out. Also, the Committee, if you want -- I don't know everybody personally, so if you just take your nameplates and stick them so that we can see them over here, because sometimes we get out of order because we're trying to see people's names.

Dr. Weinstein.

DR. WEINSTEIN: Two very quick questions. One, we're requiring a board-certified neurologist to write the first prescription, yet the whole discussion that we're having has nothing to do with neurology; it has to do with ophthalmology. And it seems that if we're going to require somebody to have

some formal training and have some test, it ought to be the ophthalmologist less the neurologist. I just throw that out there.

And second is a question about the OCT with the layer thinning. That strikes me as being an anatomic something dropped out, cell loss, fiber loss, something. And is there any reason to presume that's reversible? And then Dr. Farkas used the term loss of functional reserve. Do we know what happens in the aging population? Is that a layer that drops out even further? And there must be 25-, 30-year follow-up on the earliest patients that have been on vigabatrin in the past. Do we have any real long-term follow up on those patients?

DR. GOLDSTEIN: So first to comment on OCT. I'll ask Dr. Robert Sergott to comment on that.

DR. SERGOTT: So OCT measures thickness. So the light is going to travel through the vitreous if it's clear, hit the

compacted area of the retinal nerve fiber layer, and then hit the less compacted area of the ganglion cells nuclear layer, and then we'll be able to measure the thickness with an algorithm.

So as far as age is concerned, there is an aging change that occurs here. The manufacturers of OCT for the stratus 3 instrument have a normal database that has been reviewed and approved by the FDA. I think it's about 720 eyes.

SPEAKER: Adults.

DR. SERGOTT: Adults from 18 to 85 years of age. And as was just mentioned, it's an adult population. And when you look at normals for the OCT, these are all age-adjusted. And they also range in refractive error from plus six dioptres of farsightedness to six dioptres of nearsightedness. So there can be changes based on the size of the eye. So this is the nerve fiber layer that we're able to measure.

Can we go to the other slides that

we showed before from Dr. Wild's data?

So then your question is is this reversible. We're still trying to figure that out.

I think there have been some cases in glaucoma where there have been changes. In multiple sclerosis and optic neuritis that I study a lot, we've seen it on rare, rare occasions.

Back to the other slides I showed before, Keith.

DR. WEINSTEIN: If I'm starting with the lower number of cells or fibers and I drop out from that, that's the functional reserve. Do we have any data on that?

DR. SERGOTT: Well, we know that we get less with age, and it is correct that that would theoretically lower our functional reserve.

Next. I need the next slide, please. So you're talking about duration of treatment with OCT. Here, we have some

patients out between 10 and 15 years. Again, defects here is normal. Defects here, 80 microns of thickness, 60 microns of thickness. This is getting down to an area where functional reserve is compromised. If another disease came along, as Dr. Farkas said, here a cumulative dose we're out to about between 10 and 15.

DR. GOLDSTEIN: So the point, though, is really interesting. So what you were saying essentially is that not only would you -- are you thinking of certification by a neurologist that the drug has indicated, but certification by an ophthalmologist that it's safe to use and safe to continue. Good. We'll come back to that this afternoon.

Dr. Chambers.

DR. CHAMBERS: I think it's important to point out the OCT is the central 10 to 20 degrees. We are not talking about the periphery by any stretch. So all the OCT you're seeing -- our current technology for

OCT -- you're seeing macular.

So that's 10 to 20 degrees. That is not 30, 40, 50, 60 where most of the field that you're measuring is.

DR. GOLDSTEIN: Very good. I'm going to let us go five minutes into our lunch break, but remember, every question is taking time out of our lunch break.

Dr. Rogawski.

DR. ROGAWSKI: I hate to stand between us and lunch, but I've got a couple of questions just to follow up on Dr. Weinstein's question. And that is are there any biological differences between the peripheral retinal and the central retina that might suggest that this would be a process limited to the peripheral retina?

Or eventually, would we expect with prolonged use that ultimately the central retinal would be affected? I'm wondering, because presumably, the peripheral retina has a thinner layer, more sparse rods and cones -- more rods. So is there a biological

basis to think that we could have this process be restricted peripherally?

DR. FARKAS: I don't think we know. Certainly, there are biological differences. There are many biological differences between the peripheral retinal and the central retina. So I think it's plausible either way.

DR. GOLDSTEIN: Dr. Jensen.

DR. JENSEN: Yes.

DR. ROGAWSKI: I just wanted to follow up also with one question for Dr. Weaver, if I could. Dr. Weaver, you mentioned that in the REMS program, at least for the adult complex partial seizure patients, that an assessment would be made at 12 weeks as to whether a patient is deriving benefit from the medication.

To me, that seems very, very important, because I certainly wouldn't want to subject patients to the substantial risk if they're not deriving any benefit from the drug. What kind of measures will you be using to determine that the patient is, in

fact, benefiting. Are there any objective criteria? How is this going to be done?

DR. WEAVER: I don't think that that's been really laid out yet. And I'll let the sponsor respond to their proposal.

DR. CUNNIFF: We've tried to leave the practice of medicine to the expert. So we would have the treating neurologist make that determination -- the epileptologist -- based on their clinical guidance and things like that.

DR. ROGAWSKI: Is there any evidence that you have that in fact, an assessment can be made in practice of efficacy of medication in 12 weeks?

DR. CUNNIFF: I think I'll ask Dr. Faught or Dr. Porter to come up and maybe walk you through how they would make that sort of decision.

DR. FAUGHT: Yes. Can we see the slide that shows the time of onset of the benefit? The dose will be escalated for adults at 500 mg per week. So you'll reach an

effective dose within five or six weeks at the most. The data show that you get a pretty fast onset of action.

This is the one that we were looking at. You can see by eight weeks the curve of benefit for all doses levels out. And you really should be able to tell at the eight-week mark, and certainly at the 12-week mark whether you're getting any benefit or not.

DR. ROGAWSKI: I guess what I'm asking is are there any reliable ways that patients can report their seizures or will you be doing ambulatory monitoring? What kinds of approaches would you use to be sure that in fact, you do have a positive response?

DR. PORTER: You know, practically, I think we'll just go seizure counts -- seizure calendars -- like we do for clinical trials or just routine clinical practice.

DR. ROGAWSKI: There's a lot of literature suggesting that the seizure counts

are extremely unreliable.

DR. PORTER: They probably are, but they're the best we've got.

DR. GOLDSTEIN: Dr. Jensen.

DR. JENSEN: Yes. This is a question for the FDA and Dr. Farkas. Given the impact of this particular side effect -- the peripheral visual field deficit and the sort of ambiguous mechanism at this point in time based on the literature and the fact that if a mechanism were to be discovered a treatment might be developed to address the mechanism and improve the outcome of patients who were treated with this drug -- does the FDA feel satisfied with the state of the literature and the efforts made to determine what the mechanism of this retinopathy is? And if not, what would the FDA propose in terms of support for such kind of research?

DR. FARKAS: Well, I think the FDA is certainly interested in finding out more about the mechanism, but I don't think that I would venture to say that we have any understanding of

how to go about doing that. I think our major concern again at this point would be with the data that we have and not being sure on the one hand about some aspects of the visual damage, and on the other hand as we had presented, being concerned with the severity of what we did identify.

DR. GOLDSTEIN: Thanks. Dr. Temple, Dr. Gardner, Dr. Crawford, and then break.

DR. TEMPLE: I just wanted to touch a little bit on the question raised by Dr. Weinstein -- why do you think this should be signed off on by a board-certified neurologist. And I think -- and then some of the follow-up questions -- follow up discussion related to that.

The whole issue here -- remember, everybody knows the drug works at reducing seizures and everybody knows it does something nasty to at least a fraction of people -- people's peripheral vision. The premise -- the thing the Committee has got to

worry about, and the thing that if the drug became available, every individual potential user and patient have to worry about is how to balance those things. Is this person refractory enough?

Can somebody intelligently decide whether the person has improved enough to merit this continued risk? And while this puts a lot of faith in board certification, surely it must be someone who is a well-trained neurologist who is going to be the person who makes that judgment, just as the people assembled in the room here are thought to be able to make that weighing.

So the logic of that -- I mean, the company can speak to that, too -- I'm sure that is what it is. I mean, who else in some ways. Now, the ophthalmologist can help you avoid disaster, maybe.

But that's a different role.

DR. CUNNIFF: With respect to the board-certified neurologist proposal we have on,

that derived from experience in Europe. So the European Medicine Agency has one restriction and that is one of-- you know, one risk management tool. And that is restriction of the initial prescription by a board-certified neurologist. So we've taken what they've done in Europe to do it here.

We also go a step further with respect to physician attestation and have them attest to the fact that they do have experience in treating patients with refractory epilepsies. So either I think either of those provisions gets us to the prescriber we want. So if we don't think a restriction by board-certified neurologist is feasible, the second part of the physician attestation that they have experience in treating epilepsy certainly would accomplish that objective, as well.

I think with respect to the ophthalmologist and the neuro-ophthalmologist, we do recognize that

they are going to be a key stakeholder in the patient's care. And that's with the mandatory ophthalmologic testing. The form -- there's an ophthalmology form that the ophthalmologist fills out. That's part of our REMS program. That form then goes to the neurologist, and then the neurologist has the ophthalmologist's opinion and they can discuss the strategy in managing that patient based on the findings.

DR. GOLDSTEIN: Dr. Gardner.

DR. GARDNER: I'd like to also ask about the REMS, and just briefly, I'll try to resist lecturing you on risk management programs. As Dr. Temple has pointed out, usually things aren't restricted to board certification because we're trying to increase access here and we try to handle it some other way. You also need to think about the fact that in Europe (inaudible).

DR. GOLDSTEIN: I think the mic went off.

DR. GARDNER: And that's not true here. And so if you put a restriction like that on the product, you'll further restrict access because insurances won't pay for it (inaudible).

Now, I'd also like to similarly think about the specialty pharmacy. It doesn't seem to make any sense if you've got this compound that needs special handling that you would think of for specialty pharmacy requirement. And so I wondered what is your thinking about a specialty pharmacy? You've already said you're going to have a special neurologist or someone who is experienced in prescribing the drug.

You are going to have a patient understandable medication guide given with every dispensing. You're going to have a patient attestation -- sorry -- an agreement with a physician. What is the point about the specialty pharmacy that would make that an element you want to pursue?

DR. CUNNIFF: Very good questions.

And to address the first one, it's not our intent either to limit access to patients who really need the drug. So we can revisit the board-certified neurologist. I do think we can get there through the physician attestation and experience with treating epilepsy.

The second part of the question -- what the central pharmacy does is it accomplishes a number of our risk management tools. So for example, we will be required to have a medication guide and we need to ensure that that medication guide is dispensed with every prescription. So if we go --

DR. GARDNER: You can package it with the product like others do.

DR. CUNNIFF: We could do that as well, but we do know that those get torn apart at the pharmacy. So contractually, we can control that.

Also, because if we have a registry program in place there's a lot of information

that will be collected -- the patient's diagnosis, the patient's prior history. We are going to be enforcing some efficacy assessments at Week 12 and enforcing for the patients with CPS the ophthalmologic monitoring. So this -- and this gives us the control over if these things aren't done-- you know, there's consequences for that for it being drug (inaudible). So this gives us more control over that.

DR. GARDNER: So you'll be compensating that specialty pharmacy or the central pharmacy for doing all that data collection?

DR. CUNNIFF: Yes.

DR. GARDNER: Thank you.

DR. GOLDSTEIN: Dr. Crawford, last question before break.

DR. CRAWFORD: Thank you, Mr. Chairman. My question is for the sponsor, as well. Thank you.

I wanted to ask what, if any, level

of follow up has been conducted by study investigators on patients who experience any vision loss. And my question is framed in terms of quality of life, because often, we certainly understand that patients will state willingness to take risks of drug access and therapeutic benefit over the potential of serious adverse effects. But related to a question asked earlier, or a comment by Dr. Kramer, are any data available for quality of life studies for those who experienced vision loss as to whether the benefit of improved seizure control did or did not outweigh the consequences of the adverse event?

DR. FAUGHT: I think that that's a very important question, and I think the actual formal data that we have is the data that I presented from Study 4020, which just demonstrated basically that patients with moderate and severe constriction of their visual fields answered the questionnaire -- were more

likely to answer the questionnaire questions positively than those that had either unimpaired or mild restrictions. I think -- so the proof of the pudding is in the eating, that the patients in Europe who choose to continue taking this drug and elsewhere have made a decision that they're willing to take the risk of the visual impairment in order to control their epilepsy. It comes down to what has a bigger impact on one's quality of life -- the peripheral vision loss or uncontrolled epilepsy.

DR. GOLDSTEIN: Thank you.

So I want to thank the sponsor, the FDA, and the Committee for the active discussion. We're going to have more of it this afternoon. I want to remind the Committee no discussions at all off the record about anything before the Committee. We'll resume at exactly 1:00.

I'm sorry about cutting into lunch, but I really wanted to give everybody a chance to ask at least one question.

Thank you.

(Whereupon, at approximately 12:12 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:06 p.m.)

DR. GOLDSTEIN: I hope everybody had a nice lunch. Let's come to order.

So this is the open public hearing portion of the discussion. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it's important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker in the beginning of your written, oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment

of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this Committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this Committee in the considerations of the issues before us.

That said, in many instances and for many topics, there will be a variety of opinions. One of the goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by me. And thank you for your cooperation.

The other thing that I'd like to -- a couple of other things I'd like to add about this is that each speaker has five minutes. We have nine open public hearing speakers scheduled. At the end of their five-minute period, the mic actually will be cut off, so five minutes is five minutes. I believe they get a -- will get a one-minute warning.

The other thing is, I know that emotions can run high, especially during this session of the hearings. People in the audience, I ask you please, no applause, just let's listen to what the people have to say so that we can evaluate it impartially.

So having said that, the first open public hearing speaker is Patricia Gibson.

MS. GIBSON: I would like to disclose that I have received support from Ovation as

with many other pharmaceutical companies for the number of educational programs that I do.

I want to thank you for inviting me to speak on my experiences with the drug vigabatrin. I have been working in the field of epilepsy since the early '70s, and early on, I recognized the tremendous need for information of education about patients and their disorder. To meet that need, I opened the Epilepsy Information Service in 1979, a nationwide toll-free information line for people with epilepsy and their families. It was the first of its kind in the world.

I've taken close to 400,000 calls myself from persons with epilepsy or close family members, mostly mothers, and many of the callers, as you can imagine, are calling because they have intractable seizures and are looking for some answer to their problem.

In 1991, I attended an international epilepsy conference in Rio, and heard about one case report of a drug that

stopped seizures in a child with infantile spasms and tuberous sclerosis, and that was very exciting to me since that is a population that I hear a lot from; they have a lot of severe and intractable seizures.

Upon my return, I received a call from a mother in Michigan who had a four-month old baby with infantile spasms and tuberous sclerosis who had failed ACTH and every other medicine that we had available in 1991. Knowing that there was little chance of her baby's seizures getting under control, I told her -- I wanted her to have a little bit of hope, and I told her about this one case report to give her some hope that there were things being studied.

"What is the name of that drug and who has it?" she demanded of me immediately. I told her that it was being studied in England, as I understood, and upon that, she said, "England. England has that drug?" and slammed down the phone. I heard from her

again in two weeks and she had the drug, but now she needed help finding a doctor who could help follow the child on that medication.

After the first pill, her child never had another seizure. Needless to say, I talked a lot about this, and it was soon that one of our own neurologists came to me and said, "Pat, I'm following a young man with an inoperable brain tumor, slow-growing, and he's working and he's starting to have more convulsions, and he's about to lose his job, and he wants very badly to keep working and to live a normal life as long as possible."

Well, his father, a physician, took him to England and got that drug vigabatrin, and this young man was seizure-free for three years up until one month before his death.

I have followed hundreds and hundreds and hundreds of patients, adults and babies, on vigabatrin, some for as long as 15

years, through this line. It has not helped everyone, but for many, it has been a miracle drug. There really are no words that can properly convey to those of you who don't have a child with seizures or who don't have it yourself, the tremendous burden that uncontrolled seizures places on the entire family -- physically, socially, emotionally, cognitively, and financially.

The statistics that they show on those slides don't tell you about the young woman who, in the middle of a complex, partial seizure, brought a skillet of hot grease to her face, but it doesn't tell you about the mother who, in the middle of a partial seizure, let the baby slip under the water as she was giving it a bath.

I can tell you that in following many patients on this drug and other drugs, that these side effects are of no consequence to most of the people I'm talking to. In fact, one of the women who -- the only woman

I know that I follow, adult, who has the visual loss that is in the severe range, I asked her one time, tell me, if you knew that it would cause this much of a problem, would you go on this drug, and she laughed at me. She said, "Pat, this drug gave me back my life."

So I hope that you will give every consideration to approval of a medicine that's available most everywhere else in the world and has been for some time.

Thank you.

DR. GOLDSTEIN: The second speaker is Mark Veasey. Hope I'm pronouncing your name correctly.

MR. VEASEY: My name is Mark Veasey. I'm from Kenosha, Wisconsin. I'm speaking on behalf of my wife. My wife had a severe head injury in 1987, which resulted in severe and intractable seizures. Every medication was tried. Nothing controlled her seizures. Brain surgery was not an option. There are no words

to describe the impact of this injury and the resulting seizures on our lives.

In 1994, our doctor recommended enrolling into a clinical trial for vigabatrin. It was a miracle drug, and completely controlled all her seizures. When the study ended, we could no longer obtain the medication. The thought of going back to constant seizures was unbearable. We found out that there was no -- that it was available everywhere except the United States, and although a major hardship on our family, we obtained the drug from another country.

My wife has been on this medication for almost 15 years, and it has made a tremendous -- tremendous quality of life. It made such a difference in her life in more ways than just seizures. It helped her depression. She is much more alert and she thinks better on this drug. She has no side effects from this drug, which she did on

other drugs she took that were approved by the FDA. She has no problem with her vision whatsoever. Vigabatrin costs us $600 for a three-month supply. It is a terrible hardship for us to buy this medication, as we have financial responsibility for both of our mothers who are elderly and in poor health.

We have appealed for the payment of this medication from my insurance company several times, but no avail. I love my wife, and as long as I am able, I will get this medication one way or another. I hope you will approve this medication not only for all our benefit, but for all the others who could also benefit, be given a chance for a normal life again.

MS. VEASEY: I also would like to mention that I see a neuro-ophthalmologist every six months and my vision is perfect. I've had no visual side effects from this medication at all in the long years that I have taken this medication, and it's really a hardship having to

pay out of my own pocket for this long a time, since the study ended. It's going on nine years.

MR. VEASEY: Thank you for your time and allowing me to speak at this time.

Thank you.

DR. GOLDSTEIN: Thank you. The third speaker is Mr. Hable.

MR. HABLE: Good day. My name is Jim Hable. I'm from Lionel Lakes, Minnesota. Thank you for allowing me the time to share my daughter, Mary's, story, and how vigabatrin has improved her life.

Mary was diagnosed with epilepsy caused by tuberous sclerosis complex in August of 2002. She was just five weeks old. My wife Eileen and I were understandably stunned by this unexpected turn in our only child's new life. The neurologist on duty assured us that her seizures could easily be controlled by medication and she could lead a typical life. Indeed, she was put on one

medication and was seizure-free for two days.

Over the next four months, her complex partial seizures continued, often as many as 20 per day, some lasting several minutes. Mary was put on various cocktails of 11 anti-epilepsy medications, some working a little, others causing more seizure activity.

In mid-November of that year, Mary started to have cluster seizures, her right arm flexing across her chest, the right side of her face tensing, lasting up to 15 minutes each. It was common for us to load Mary with rectal injections of valium almost daily. Between the valium and the seizures, Mary's brain was constantly tired. She made virtually zero cognitive progress for a month, a month of the most important time for cognitive development.

Eileen and I were worried that the clusters may be precursors to the infantile spasms, an even more devastating type of

seizure that can actually cause a loss in brain development. Our neurologist assured us that there were no signs of infantile spasms on Mary's EEG, however. We expressed to our doctor that we wanted to put her on vigabatrin. We got the name of a pharmacist in the Netherlands that would fill prescriptions and send it to the States in legal quantities. Our pediatrician was kind enough to write a prescription -- we faxed it off to Amsterdam at the cost of $1.75 per pill plus shipping. We were spending over $100 a month.

Mary took her first vigabatrin on December 18th. On Christmas Day, she had zero seizures, the first day in her life after those initial two days. She went from 10 to 20 complex partial seizures per day to two to four simple partial seizures a day. Immediately, we saw Mary's ability to learn show vast improvement. She started to babble more, she would understand simple directions

and recognize faces.

Within a few months, she was crawling, and one day, she spoke her first word: dada. Mary continued to develop, and after a year and a half on vigabatrin, she was still having simple partial seizures. Given the cost and the supposed side effects, we weaned her off of vigabatrin. Within days of taking her off of vigabatrin, her seizures became more intense and more frequent. Eileen and the doctors decided that a tuber resection would be the best route to go for elimination of Mary's seizures.

Mary had four tubers resected in December of 2005. She was seizure-free for three months. Due to complications during surgery, she lost some function on her right side, including fine motor skills in her hand, and her ability to form words with her tongue and lips. She also lost balance and strength in her right leg, ankle, and foot. She didn't walk until after her third

birthday.

I often wonder if we would have considered surgery if we could have kept her on vigabatrin long-term. If she didn't have surgery, when would she have walked? Could she speak better? Would she be able to write her name by now?

Mary's seizures slowly began to increase over the next two years, to the point she was having three to five a day, and we were noticing that the simple partial seizures were moving to complex partial seizures again. We found ourselves at our neurologist's office in December 2007 trying to decide the next plan of attack. Mary had just had an EG with no new activity.

Eileen and I told our doctor we wanted to go back on vigabatrin. He explained that Mary would have to have an ERG every six months to ensure no retina damage if she had. This was not considered an option when she was on it the first time, at

least we were not told it was an option. Anesthesia during ERG was a small risk compared to her having complex seizures again. Within a week, we had procured some vigabatrin, within two days, Mary's seizures went from three a day to one every two weeks.

2008 was a delight. Mary's learning at a higher rate, she speaks new words almost daily, her intelligence is quickly improving, so did her ability to problem solve. She has more energy and is just a happier little girl. She started kindergarten this year, and spends most of her day in the typical classroom. With a little help, she spends most of her days like a typical kid.

Mary turned six years old last year. We had a big party. For that weekend, she was the center of attention and she loved every moment of it. She had no seizures. The best days of her life, the most productive days of her life, have been when

she has been on vigabatrin.

This is why I come here today and ask you to approve the sale and distribution of this very important medication in the U.S. It will changes the lives of thousands.

Mary --

DR. GOLDSTEIN: Thank you. Our next speaker is Dr. Mattson.

DR. MATTSON: Good afternoon to the Committee and others. I'm here as a private citizen, but also as a representative of the J. Kiffin Penry epilepsy programs. And I'm professor emeritus at Yale University, but I do not represent Yale at this hearing. Emeritus, in case any of you professors are wondering, means you can keep doing the same amount of work for a fraction of the salary.

I've been treating people with epilepsy for about 50 years, and I can't really add a lot to what Dr. Faught and Dr. Porter have said about the problem of epilepsy, although I'll return to that in a

little bit.

I have had experience with use of vigabatrin, and indeed, I used it for 20 years. The first studies were those that we've heard reviewed by the sponsor, the add-on trials, and then we began doing trials of nuclear magnetic resonance spectroscopy to understand what was going on in the brain when we gave people vigabatrin. And incidentally, for the person who asked that particular issue, it was true that three grams seemed to be optimal, and that we didn't see a greater increase in GABA -- we were measuring GABA in the brain using this technique -- and indeed, we started the drug at even as high as six grams in one dose to look at the effect it would have on the brain, but three grams was the optimal dose that we found in terms of GABA. Now, whether that surrogate marker translates to efficacy, I can't say.

But over the years, I saw a lot of

people. The first half of the group of 40-plus had no visual fields done, but then the report came out of the visual field problem, and so we conducted them in the NMRS study, and for some reason or other, there were only two people who had a visual field defect, one of whom didn't know it.

The other one complained of the visual field defect, and has been indicated before, this person had a field defect to start with due to a bleed in the occipital lobe as an infant. But it brings up the issue is that thought controlled and putting him on vigabatrin resulted in complete control -- he began to drive, he was working at the family business, and when we recognized the visual field defect, I told him he really needed to come off the drug, and he said, I don't want to do that.

So I sent him down to Greg Krauss at Hopkins who had a lot of experience with this, and it was thought that perhaps he

could stay on the drug, but I ultimately took him off and happily he responded well to adding Lemictal (?), but it's a good example. He was willing to stay on the drug because it had so profound an effect on his life.

And we see similar kinds of things -- epilepsy is a very serious condition as is evidenced by the recent Travolta death, and my stepdaughter in high school had a classmate die of a seizure in the same week, so it's a serious risk/benefit issue, even though obviously, there's risk.

In terms of speaking for the Penry Group, this is a group of neurologists, epileptologists who have been together for 20 years, and over that period of time have trained neurologists -- some quarter of all the practicing neurologists in the United States have gone to that program -- and the faculty is very distinguished and very aware of epilepsy and participated in most clinical trials.

And basically what I would like to summarize is this group of very experienced, wise people are well aware of the side effects of this drug, but they feel in this population, a risk/benefit makes it their recommendation that this compound be approved.

Now, one issue came up that I would like to add my own personal opinion about, the word "intractable" epilepsy, and I think intractable epilepsy requiring or indicating a use of a drug like vigabatrin should not be simply a trial of two or three drugs. I would personally, if I used the drug, I would use every available drug except perhaps felbamate first.

I might not use neurontin or tiagabene (?) if they had already failed Lemictal and kepera (?) and topiramate, but I would use most of them before doing that, and in that case, however, it is very valuable to have access to something that can make a

significant benefit.

DR. GOLDSTEIN: Thank you. Joyce Kramer.

MS. KRAMER: Please start my slides before the timer. I represent Epilepsy Therapy Project, a non-profit organization founded because of the wide unmet needs in the epilepsy community. And my theme today is: give patients a choice. Vigabatrin may be far less devastating than epilepsy surgery, which is the last step for those who have intractable epilepsy.

Our mission is to support development of new drugs. People with epilepsy do reach out for information. You're not talking to a vacuum. Our website is viewed by 200,000 people a month. Our professional website is viewed by 25,000 people a month. People seek information; they get information on our website as in others. We provide unbiased information about all the good and all the bad that

relate to each new epilepsy drug to be available for patients. There is a clear unmet need. In this country alone, a third of people live with uncontrolled seizures whether it's having failed one, two, three, four, or five medications.

You've heard all about this from other people who've spoken before me, what it means to have uncontrolled epilepsy. I'm proud to say I worked with Dr. Massen (?) for many years, and we ran a big surgery program. By the time people come to surgery, their lives are really broken. As a quality of life researcher, I can tell you, we want to prevent that. We want to get people before that point.

Early studies have demonstrated, as well as more recent studies, the efficacy of vigabatrin. Keep in mind that approximately one third of people who stated vigabatrin improved by 50 percent, the gold standard for efficacy. And many, as you have heard,

became fully controlled. This obviously is an issue where the adverse effects are not affecting 100 percent of people. You may feel that 25 percent is a very large proportion, we don't know whom -- it's probably a genetic factor, there's some allele that is predisposing certain people to develop visual field defects. This is not the time or place to figure out the genetic disorder, but to give people a chance, give people a choice.

I have an example for you, but I'm not going to go into great detail. This is a case described by a medical-legal expert in Australia -- similar to the two cases we heard about earlier -- someone who had uncontrolled partial onset seizures as an adult, went on vigabatrin, was informed he had visual field defects, preferred to remain on treatment.

The physician, the medical-legal expert, considered the patient "an autonomous

agent," who could make this decision, and therefore he stayed on the drug because the drug was effective and epilepsy had been devastating to him.

It is the patient's right to make decisions. Surely, that's the hallmark of our American way. We urge the FDA to give patients this choice, particularly when there are so many drugs on the market that cause mortality, not just morbidity.

We've talked a little bit about felbamate causing aplastic anemia, valproate can cause hepatic failure and pancreatitis. Topiramate, I had just read on the web -- 67 percent of children have a metabolic acidosis, just to mention a few of the epilepsy drugs, not to mention clozapine, which can cause cytosis, touzabrebe (?) which causes PML; immunosuppressants, which have a variety of short and long-term severe adverse effects.

There are so many ways in which

patients can be given a choice as to what to take, and to go back to the immunosuppressant and even to disabri (?) for MS -- yes, there are other drugs available, but FDA has allowed these drugs that cause mortality to be available.

They have not rescinded the approvable letter, they simply have included big black boxes and allowed the decision to be made with a discussion between the patient and family and the physician. I happen to disagree with the need to have full testing in advance of starting the drug. My preference is to give all comers three months trial. Within three months, you know if the drug will work. If not, stop it. If it does, then go into the testing. I think you will do no harm if you proceed along that route.

Again, I will end with my point: Give patients a choice. This is better than epilepsy surgery. Thank you very much.

DR. GOLDSTEIN: Thank you.

Mr. Crossland.

MR. CROSSLAND: Good afternoon. I have not received any financial compensation from Ovation or its competitors. It is my privilege to be able to speak to all of you today as an advocate for people who are affected with refractory epilepsy, and the urgent necessity to have access to as many medications as possible in the hopes of finding the right medication or combination of medications which will aid and control in the debilitating seizures which accompany most refractory epilepsies. The only way I know how to do this is to relate my story.

My journey here to this point in time began on June 6, 2008, seven months ago, when my son Scott died from SUDEP, Sudden Unexpected Death in Epilepsy. He was eight years old and had just completed the first grade.

I'd like to tell you about Scott.

I brought his picture with me, which is up on the screen for you to see. The picture is Scott's class picture, taken in the fall of 2007, just after the school year got underway. Scott loved going to school. If it were up to Scott, he would have attended school every day. If Scott was sick or his severe seizures precluded him from going to school, Scott was very sad because he could not be with his friends.

When Scott was 11-1/2 months old, he suffered his first statis (?) tonic-clonic seizure. It lasted about 90 minutes. I was at work when it happened, and it was heartbreaking for me to arrive at the hospital not knowing what had happened and to see my little baby still in a seizure with a breathing tube coming out of his mouth.

Finally, after the third statis tonic-clonic seizure within two months, Scott received an epilepsy diagnosis. Soon afterwards, Scott started seeing Dr. Doug

Nordley, head of pediatric epilepsy at Children's Memorial in Chicago.

After about a year of trying a few different medications, Dr. Nordley told my wife and myself that Scott's symptoms were consistent with severe myoclonic epilepsy in infancy, or SMEI. Today, SMEI is better known by many neurologists as Gervais Syndrome, a catastrophic refractory epilepsy.

We were told that not many FDA-approved medications were available to treat children with this rare form of epilepsy. It wasn't until almost two years later, when Scott had tried and failed almost all FDA-approved medications available for his diagnosis, that we learned about the difficulty of acquiring, and the cost involved with, medications approved in Europe and Canada which have already been proven safe and effective for children with Gervais Syndrome.

One of the hardest issues for

neurologists and epileptologists who handle patients with refractory epilepsies is that no two patients react in the same way with the same medication. What worked well for my son may not work well for another child with the same type of seizure activity. All too often, what is required is a lot of trial and error. Of the two medications from outside the country which Scott tried, he failed one, and the other was a helpful part of his daily regimen for the last few years of his short life.

In my experience over the last seven-plus years with all the medications my son tried, the big concern of Scott's epileptologist was the possible side effects. Scott was one of those people who got many of the side effects that were possible with each anti-convulsive medication. I wish I had the number of all the medications my son tried over the years. He had several failures as well as several meds that worked okay for

him. When Scott passed away, he was on four different medications, twice a day.

I mention the number of meds my son was on when he passed and those he had tried over the years including those from overseas, as well as mentioning the possible side effects to make this point, that people with refractory epilepsies need as many medications made available to them as possible.

It is only by trial and error that they will know what will work and which medications will not help in controlling their seizure activity. Yes, there's a small risk of side effects, but there's a small risk of side effects in all prescribed medications. One cannot watch television these days nor read a magazine, and not come across advertisements for FDA-approved medications, all of which mention the small risk of potential harmful side effects.

In the case of anti-convulsants, as

with all prescription medications, the ultimate decision of whether or not to try a medication is up to the doctor and the patient or caregiver.

In my experience with my son, his epileptologist fully discussed all the pros and cons of each particular medication, including all the possible side effects. It was then up to my wife and myself to make the decision whether or not to have our son try that particular medication. Most of the time, the potential benefit of better seizure control greatly outweighed the small possible risks involved. Epilepsy is a cause which is very close to my heart, and I would like to thank you for giving me the opportunity to speak to you all today.

DR. GOLDSTEIN: Thank you.

Dr. Gattone?

DR. GATTONE: Good afternoon. My name is Phil Gattone, and I do not have any financial relationship or receive compensation from

Ovation Pharmaceuticals or its competitors. I am an employee of the Epilepsy Foundation, and the Epilepsy Foundation has received financial support from Ovation and its competitors.

I'm also the parent of a child with epilepsy who took vigabatrin for five years for treatment of intractable complex partial seizures.

Our son Phillip was born in December of 1986. He met all of his initial milestones -- he walked early, he talked early, he read when he was four years old. Then, on April 11, 1991, at the age of four, his world changed. He had his first seizure. It was a generalized tonic-clonic seizure, lasting a long time, stopped only as he was put purposefully into a drug-induced coma in the emergency room of our local hospital.

He recovered, and after several days in the hospital, Phillip, his mother and I returned home with little understanding of what was ahead for him.

In the months and years that followed, Phillip experienced cognitive decline as the seizure frequency and severity increased. Phillip was tested by a pediatric neuropsychologist at age five.

The tests showed that despite the many seizures he was enduring, his gross IQ score was 115. However, only one year later at age 6, his IQ was 72.

He had daily complex partial seizures, many secondarily generalizing. We sought what we felt was the very best care for him. Based upon his seizure type, his spike and slow wave EG during rest, his lack of response to any and all medications that we tried, and his cognitive decline, Phillip's prognosis was poor. Great physicians had to tell us they were powerless to help control Phillip's seizures.

We continued to pursue treatment options that might find control for Phillip. Throughout this journey, Phillip had

thousands of seizures. In a visit with an epilepsy specialist in 1992, we learned Phillip might be a candidate for surgery. The physician explained the risk to us, and we had the surgery done in 1993. Unfortunately, three months after the surgery, Phillip's seizures returned.

Then we found out about vigabatrin. We understood the potential risks and we decided to try vigabatrin. We were amazed, and Phillip was fortunate, as we watched Phillip's seizures for the first time come under much greater control. Not only did his seizures nearly stop completely, his EEG was cleaner than it had ever been. It was not free of spikes, but there was no longer a continuous display of abnormal epileptic activity, as had been the case in virtually all previous EEGs.

Vigabatrin gave Phillip the gift of time, time he needed to develop without constant seizure activity interfering with

his learning. It's amazing to watch how much more effectively a child can learn when they are free of the bombardment of seizure activity.

Phillip remained on vigabatrin for five years, 1994 to 1999. After a tremendous amount of perseverance and commitment on his part and on the part of the medical, education, and social support teams, Phillip improved. He began to actually catch up to his peers. He participated in school and sports activities. He graduated high school in 2005 with honors -- I'm really happy.

This week, he begins his final semester as a four-year senior at Southern Illinois University. He will graduate May 9th with a degree in computer engineering. His senior project is designing and building a brain-computer interface, whatever that is.

Every day, I work with people with epilepsy who have not been as lucky as

Phillip.

I respectfully request that you approve this drug and give people the gift of time.

Thank you.

DR. GOLDSTEIN: Thank you. Maybe we can come and get him to get these mics to work.

Next speaker is Dr. O'Donovan.

DR. O'DONOVAN: My name is Dr. Cormac O'Donovan, and in the interest of full disclosure, I've received assistance with travel expenses from Ovation. I've also received support from pharmaceutical companies for drug studies and consultations in the past.

Today, I represent, as a physician treating epilepsy who has -- was born here and traveled -- went back to live in Ireland at an early age, and received a medical education and initial neurology training there before pursuing residency training at the Cleveland Clinic, and have been a faculty member at Wake Forest.

My purpose is twofold in this brief presentation: To first of all give some of my personal experience, but also to introduce you to some patient testimonials of a colleague of mine, Dr. Normand Dellante, who is director of the National Epilepsy Center in Ireland, which I was initially involved with, and who has a broad experience and a large experience treating with vigabatrin.

Here, we can -- by way of introduction of the video, which is two of Dr. Dellante's patients, both are now adults who developed epilepsy as children, where refracting two medications, the initial medication they tried in multiple different combinations, and are now seizure-free on vigabatrin.

In both cases, decisions to maybe discontinue the vigabatrin resulted in recurrence of the seizures, so they remained on it for many years.

They have had visual testing and

close neurologics, and both have by Goldman perimetry were being characterized by moderate visual defects; however are without visual complaints, and are well aware of the risks and have continued on the drug despite that.

Could we play the video? You will see here a testimonial from the mother of one of the patients and then one from one of the patients themselves, and then Dr. Dellante is going to offer some comments.

(Video is shown)

SPEAKER: It takes a long time for ambulance to arrive and then go back to a hospital again. And his life was very curtailed. And, I mean, getting involved in the sport was really -- was really not a possibility. Those who organized the games really weren't prepared to take on the responsibility. And looking back on Frank's life when he was younger and he was having a lot of seizures, it's true to say that he was never

invited to birthday parties because no one wanted to take responsibility. Our lives have been transformed because of Sabril, because without it, we would be living the life of total anxiety. Sight impairment has not affected the quality of his life in any way whatsoever. Frank works physically and he will work with machinery. He's very adept at doing that. He works on the computer. He reads his books. He reads correspondence. In no way does he need glasses.

SPEAKER: Sabril has completely changed my life.

SPEAKER: We have experimented with reducing the Sabril, and when it was reduced, things became messed up again, so the Sabril was put back to square one, or it was, and things improved again.

SPEAKER: Is not a thing I know, (inaudible) I don't know (inaudible). I mean, I get it checked and to say maybe it's very, very slight change but I can't notice (inaudible) and

it's -- it's not there. It's negligible as far as I can see and as far as I'm concerned. If I had to do it again, I'd take Sabril.

SPEAKER: There are patients who remain on vigabatrin despite some visual (inaudible) constriction and having had discussed it with the patients and the relevant family members, remain on vigabatrin because it's improved their quality of life. And of course, these type of decisions are made in conjunction with the patient and their families.

(End of video)

DR. GOLDSTEIN: Thank you.

Dr. Schachter?

DR. SCHACHTER: Thank you very much and good afternoon. My name is Steve Schachter. I'm the president of the American Epilepsy Society, and professor of neurology at Harvard Medical School, and I'm here to speak in support of the approval of vigabatrin for treatment of refractory complex partial seizures in adults.

I'll just say a couple words about

the American Epilepsy Society, the need for new therapies for patients with refractory complex partial seizures, a few words about the manner in which physicians, along with patients, decide on which seizure medications to take, a couple words about vigabatrin and my personal experience and then to sum up.

The American Epilepsy Society, which was established in 1936, promotes research and education for professionals dedicated to the prevention, treatment and cure of epilepsy. Our annual meeting is the premier conference for exchange of information about the diagnosis and treatment of epilepsy.

The members of the American Epilepsy Society reflect a broad multidisciplinary community, including epileptologists, who are neurologists who specialize in the treatment of epilepsy, neurosurgeons, allied health professionals, neuroscientists. We maintain very close

relationships with other professional organizations, including the American Academy of Neurology, the Child Neurology Society, and the International League Against Epilepsy.

As we know, despite available anti-epileptic drugs, a large proportion of patients with epilepsy still have seizures, and those with complex partial seizures are particularly resistant to available anti-epileptic drugs. The possible complications of refractory complex partial seizures include death and life altering injuries, and therefore, there remains an urgent need for new therapies for refractory complex partial seizures.

Epilepsy clinicians approached the clinical decision-making, as we heard with Dr. Dellante, based on their individualized assessment of the risks and benefits of treatment for particular patients. This is an individualized process that is difficult

to reduce down to formulas or guidelines but it involves an assessment of the possible risks of the drug to a particular patient, and the possible consequences to that patient, and at the same time, the potential benefit of that drug to that patient and the potential impact of that benefit if it were to occur on that patient's quality of life.

As I mentioned, this risk/benefit assessment is individualized for each and every patient, and it's based on the available information about therapies, clinical experience and training of the clinician, and detailed knowledge of the individual patient's circumstances.

Epilepsy clinicians make these risk/benefit assessments every day in their practice. They do this for FDA-approved drugs with potential life-threatening or life-altering side effects; they do this for surgical interventions, again with potential life-threatening or life-altering

complications.

As we said, there is an urgent need for new therapies for refracted complex partial seizures. Vigabatrin, in my opinion, represents an important new treatment option. Published clinical trial data support its use in adults with refracted complex partial seizures. The potential side effects are well-understood and well-described. There is substantial use in clinical practice outside the United States, as we just heard from Dublin, Ireland, to inform the risk/benefit assessment and it has a unique mechanism of action.

Over the past 25 years, I've cared for thousands of patients with epilepsy and have personally seen, along with many of my colleagues in this room, the devastating effects of refractory complex partial seizures on patients and on their families, and at the same time, I have been privileged to personally witness the remarkable

turnaround in the lives of my adult patients when their complex partial seizures come under control.

So to sum up, the prevalence, complications of refractory complex partial seizures are substantial, requiring new therapies. Epilepsy clinicians base their treatment decisions on individually applying risks and benefits to patients. The American Epilepsy Society educates prescribers about the diagnosis of epilepsy and the risks and benefits of treatments.

Vigabatrin represents an important new treatment option for adults with refractory complex partial seizures.

DR. GOLDSTEIN: Thank you. And I want to thank each of the open public hearing speakers for sharing their thoughts, their experiences, and their perspectives. Everybody on the Committee is involved in patient care in one way or another. We're all people people, and hearing your perspectives is extraordinarily

helpful and important.

The open public hearing portion of the meeting has now concluded, and we'll no longer be taking comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee as well as the public comments.

So we have a fairly extensive number of questions to deal with, and as we said earlier, there's actually -- the way it was set up was for votes on each question, but the way this works is that when we vote, there actually has to be a roll call to go into the record, which would mean that if I started now and we just continued doing this, we would do nothing except take roll call votes and have no chance for discussion.

It's actually the discussion that's the most important thing for the FDA to hear. The vote is important. I don't want to underestimate that, but it's the discussion

and the thoughts of a group of people with particular expertise that are otherwise uninvolved in this to -- that they really need to hear.

Again, we had several general questions that we started the morning with, and I just had them put up again now just to keep that perspective. If you looked at the list of questions, there, again -- they were ordered based upon thoughts before the meeting, but I think what I'd like to do is actually change the order a bit from the way they're listed there and sort of combine them, for both efficiency and also for logic.

What we'd like to do, if you could put up Question 2 first -- there we go. So what I thought we would do is take -- the Committee has their list of questions -- Question 2 and Question 3 sort of together and deal with them first. If the Committee can't envision any combination of patient populations and conditions that would

support approval, then we've got nothing much left to talk about, so I thought we would get -- try to deal with this question first, and as part of the discussion, again, under Question 3, is what would the appropriate population be, and should additional effectiveness or comparative data be obtained in this population.

Now, the other thing that we have, and one -- again, the nice and the bad things about this is we have a very large committee here, and it was done on purpose to gather a lot of expertise, so given the nature of this first question, what I'd like to do is have the epileptologists -- give the epileptologists in the group and on the Committee an opportunity to talk first and give their perspectives given what we've heard from both the FDA, the sponsor and the public.

Dr. Weinstein? And everybody, please, again, tilt your nameplates this way

if they're pointed differently.

DR. WEINSTEIN: I'm always looking for a new drug. Like everyone else, I have lots and lots of patients who don't get better with whatever I give them, whatever intervention that we provide, and I don't think for me, at least in the adolescent population, the adult population, that there's any question that there are patients that get better with vigabatrin.

And having said that, I suppose it comes down to the cost of the vigabatrin. And the morning primarily was focused on the ophthalmologic consequences of drug, and, yeah, I think it's right that patients make an informed consent as to what drug they want to use, but I have reservations in the sense that the first speaker this morning defined refractory epilepsy as having failed two drugs.

And those of us sitting in this room certainly wouldn't accept that as being refractory epilepsy. But if that's what the

world is moving towards, if that's what corporate America is preaching, that's what academics is preaching, then all of the sudden vigabatrin becomes available to a population -- that, I wouldn't necessarily consider refractory. Certainly the examples that were provided of individuals failing 10, 12, 15 drugs -- my patients -- clearly, it's one more to be utilized. It gets down to where in the pecking order the drug goes, and I don't think many of us, at least in this room, would say it's number three or four.

But how do you communicate that to the rest of the world that are out there trying to make these decisions, and oftentimes, decisions are made not by science, because oftentimes there's no science, but by the last drug rep who happened to visit the office or what my experience was the last time I used the drug, and I forget about all the times that things didn't work.

So the issue to me is, where in the pecking order it goes, and if we're -- how do you keep it from moving way up front, and to be honest, I can't think of a drug that's come out where we're quoting 50 to 60 percent side, 50 to 60 percent patients are going to have irreversible ophthalmologic changes.

Now, again, I could buy it if you could demonstrate that efficacy is far better than anything else that I have. That would warrant the risk. That would warrant the risk of using it up front. But 50 to 60 percent having potential irreversible damage to their eyes, though we have no idea what the real natural history is, no idea of who's responsible if a patient does lose vision, and what kind of resources are going to be available to take care of them.

The only other question that I had, to take a little side step, was that in putting together the little blurb as to what's going to happen, we're going to

require patients to see an ophthalmologist in order to get the drug, and we have patients that are living hundreds of miles away from real ophthalmologists and perhaps real neurologists, and all of a sudden, it's now written that the company is going to withhold the drug from them, they're not going to have it available. What happens to those patients if it's been effective?

Who cares if it's been ineffective, but who cares if all of a sudden, there's not the money to pay for all these fancy ophthalmologic tests that were mandated in order to get the drug, and we withhold it from them? Just the cost of the drugs that were mentioned here, $600 every three months, there's certainly no sense that any insurance company with other new drugs that are coming out this year, are going to put this high on the list of funding it, and we're still left where we are now of providing a very expensive new drug.

It may not be as expensive as some of the other ones, but it's expensive.

So yeah, it works. How do you keep it from patients who should fail some other drugs? That, to me, is a key question. And what happens when indeed patients lose significant-enough vision that no longer to take care of themselves? You know, what we've heard is those patients who did well, their seizures were controlled. Those patients who did well, they had the visual field deficit, but it didn't interfere with their life.

Where are the patients that we've heard about that did have deficits? What do we know about them? And what do we know about them after the drug is stopped?

So I like the drug. I've used the drug. I've used lots of drugs. To me, it's just an issue of how do you control where it's used in this whole mix. The FDA has stipulated based upon -- I guess 024 and

025 -- that they feel the drug is efficacious. I don't know if it's effective, but efficacious. Those studies were done before many of the currently approved drugs for partial complex epilepsy were available.

So how does the -- from the epileptologist again -- how does that -- how do you factor in that is -- is the information that's available, is that sufficient to show effectiveness in it currently? Do more studies need to be done? Again, these are the sub-questions of the primary question that we're trying to address right now.

I don't know that I've readily convincing data that any one anti-convulsant is better than any other anti-convulsant. The numbers that were quoted in terms of decreasing seizure frequency at 50 percent or turning it off for six months at 15 percent, boy, they sound just like every other new drug that's come out.

So most of us pick drugs -- I can't say most of us, I'll speak for myself -- by what are the possible side effects, how bad are they, and how often do you see them. And then, as indeed the patients have to make an informed consent, but the problem is, patients never make informed consent. They're told, they're pushed in a direction.

DR. GOLDSTEIN: Dr. Rogawski?

DR. ROGAWSKI: Thank you, Mr. Chairman. I'd just like to address that question that you asked about how this drug stacks up to some of the older drugs and perhaps some of the newer drugs, but first, I'd like to say that I very much favor having as many options as possible to treat patients who have epilepsy. It certainly is a devastating problem, and the more drugs, the better.

But I think we have to put vigabatrin into perspective, and since the studies that were done that were submitted to the FDA that we've heard about today were

carried out, a great deal of information has developed from work abroad, particularly in Europe, to try to understand how effective this drug is -- and I think there is no question that the drug is an effective treatment for partial seizures in adult patients.

But the question is, how does it stack up with some of the other options that physicians have. And of course, this is extremely important because the sponsor is proposing that we use this medication in those individuals who have responded inadequately to other medicines, and as Dr. Weinstein says, where should we put this in the pecking order.

And from my review of the literature, it seems to me that while vigabatrin is effective, it's not terribly effective or necessarily more effective than other options that we have. There were several monotherapy trials that were done in

head-to-head comparisons. One of the most important ones is by Chadwick, which was published in 1999, which was a monotherapy trial, fully controlled double blind, placebo controlled -- head-to-head study, not a placebo controlled study, but a head-to-head study between vigabatrin and carbamazepine and the conclusion there was that while vigabatrin seemed to have somewhat less side effects than carbamazepine, overall, the efficacy was not as substantial as carbamazepine.

Several uncontrolled studies done in a head-to-head fashion also came to this same conclusion. So I think fundamentally, we don't have a magic bullet here; we have another option that may provide some utility for some patients. And so I think that we need to put this into perspective when we think about it in terms of the risks.

I certainly would like, if this drug is approved, to have a better handle on

in fact how efficacious it is, specifically for those patients who are refractory to current medications. I don't think we have that information now. Dr. Katz addressed that in his earlier question about how effective is this drug in those patients who seems to have failed a large number of other medicines, and we just have the beginnings of that information. It seems to me that we don't know this drug is necessarily any better for the refractory patients, which are the ones that are going to be treated.

So we know it's effective, but do we know it's effective in refractory patients more than other options that are available. I don't think the evidence is there to support that.

DR. GOLDSTEIN: Dr. Dure?

DR. DURE: Yes, thank you. I am struck by the -- the tenor of the debate is really about risk versus benefit, but Dr. Sleath mentioned something earlier that we had not

amplified very much, and that has to do with the issue of, is this -- are we talking about adults or adults and children? All the testimonials have really dealt primarily with children, and if we approve -- if this drug is approved for adults, I think we all know that children will then be given this agent, and the issue then of child assent, I think, becomes very important, because we're talking about what the best I can gather is, that the visual loss is probably permanent.

And so subjecting children to that risk perhaps for treating them for years, again from the testimonials, I think this is a -- we're going to have to in some way ensure that there's a mechanism to where children are able to provide assent or age-level assent that's appropriate. And I don't know if this Committee really thinks about this very much, but there is ample literature in asthma as well as in oncology for these types of processes, and this is

something that will have to be considered if we do indeed decide that populations are -- it's approvable.

DR. GOLDSTEIN: Dr. Temple? Sorry.

DR. TEMPLE: Off-label use is always a sensitive matter. We have labeled a lot of drugs for psychiatric conditions and so on, where we pretty strongly recommend that they shouldn't be used in children because they haven't been shown to work, but we don't consider withdrawing them from adults for that purpose. And I guess I would sort of urge that tomorrow's going to be the children one, and you probably want to think about that.

Maybe this is part of the discussion -- I'm not saying it isn't -- but the harder question, I think overwhelmingly, is whether this should be recommended for adults today and then children tomorrow. We haven't figured out a way to stop people from doing what they want to do.

DR. GOLDSTEIN: Dr. Balish?

DR. BALISH: Just some brief comments. I can conceive of my own mental calculus in trying to decide what patient I was going to use this medication on, but I can't conceive of a formalized written calculus for this same kind of thing.

I can say a patient has tried everything that I have ever used before, and I certainly have patients who have gone through many drugs. I can't see how we can make an adequately safe determination of this.

I do think that having the option would be useful, one more drug. Every new drug that I've seen accepted, I've had one or two patients, a couple of patients, who've been completely controlled and it's made a difference. Can we make it safe enough? I'm not sure yet, based on today's information.

DR. GOLDSTEIN: Thank you. Let's try to deal with -- I'm sorry. Have I missed somebody? I'm sorry. So what let's -- let's

just get a sense for this first question first. Can the Committee envision any combination of patient population and conditions of use that would support approval? We're not saying that it should be approved, just can you envision any combination of patient population or conditions which would support approval given what we've heard?

I don't want to do a formal vote if we can avoid it.

DR. KATZ: Clarification of that question.

DR. GOLDSTEIN: Sure.

DR. ROGAWSKI: Do you mean, can you define today what that patient population is? Are you asking us, is there a patient population? Or are you saying, can we define it?

DR. KATZ: I think the subsequent questions will get at the question of, if you do think it's possible, what are the conditions, should they be truly refractory, should they be

shown to respond where they haven't responded to other drugs and had that comparison? This sort of thing. Should they be monitored every three months?

So later, I think we need to talk about the details, but right now, what I meant by this is, can you in effect -- I'll ask the opposite question. Do you think that no matter what we did -- restrict the population, restrict the labeling, safety monitoring -- it couldn't possibly be approved? If you can envision in your minds -- at the moment -- I'm not asking you at the moment what those conditions are, but if you can envision conditions under which it can be approved, then the answer to this question is yes. We'll get at what those conditions are. It includes the question of getting more evidence.

I want to know if you can just in your minds think of data you might want that we don't have yet, it includes -- later, we

ask you the question, given what we have in hand now, should it be approved? This question is sort of a thought experiment. Can you imagine any scenario, even data that we don't yet have, that would sort of --

DR. GOLDSTEIN: So Russ, in some way you're asking whether the toxicity is so bad that you can't imagine approving this no matter what you knew?

DR. KATZ: That's what I was saying. I was asking in the opposite direction.

SPEAKER: I would think a vote would be useful at this juncture, in a sense. Could we possibly consider that?

DR. GOLDSTEIN: That would be fine.

So if we're having a formal vote, then the question is, can the Committee envision any combination of patient population and conditions of use that would support approval?

So let's go ahead and deal with that. And you have your little buttons down

there. What we have to do is everybody has to press their little button, and hopefully this will work, and then once that's done, then Dr. Ngo has to go through and do a roll call to verify the vote.

SPEAKER: Press and hold or just press?

DR. GOLDSTEIN: Just once, as far as I know. Our technological wizards, just once? I know it's just flashing here. Keep pushing it. What is this, Chicago? Vote early, vote often?

SPEAKER: Does that give us more votes?

SPEAKER: There are two more people who haven't voted. One more person.

DR. GOLDSTEIN: Did it work? You've got all the votes? Okay, cool. Now what? Now we have to go through and do the roll call, so we'll start at that end. Remember we have some -- huh?

SPEAKER: We still need you to state your name and your vote for the record.

DR. GOLDSTEIN: Yeah, we have to go through, everybody has to state their name and vote formally, and then we'll put up what the result was.

No, we have to do it this way, unfortunately. So now what we have to do is everybody has to go through, say their name, and how they voted. This will be a big surprise. You can see why I wanted to try for the hand waving instead first. Okay, down -- let's start down at that end.

We'll go this way this time. So I guess the first voting member is Dr. Hirtz, and we'll travel from there.

DR. HIRTZ: Deborah Hirtz. Yes.

DR. MIZRAHI: Eli Mizrahi. Yes.

DR. WEINSTEIN: Steve Weinstein. Yes.

DR. JENSEN: Frances Jensen. Yes.

DR. CHUGANI: Harry Chugani. Yes.

DR. DURE: Leon Dure. Yes.

DR. SNODGRASS: Wayne Snodgrass. Yes.

DR. GORMAN: Richard Gorman. Yes.

DR. HECKERT: Richard Heckert. Yes.
DR. WEST: Constance West. Yes.
DR. ROGAWSKI: Michael Rogawski. Yes.
DR. VEGA: Marielos Vega. Yes.
DR. SLEATH: Betsy Sleath. Yes.
DR. GOLDSTEIN: Larry Goldstein. Yes.
DR. JUNG: Lily Jung. Yes.
DR. RIZZO: Matt Rizzo. Yes. Four times.
DR. BALISH: Marshall Balish. Yes.
DR. LU: Ying Lu. Yes.
DR. van BELLE: Gerard van Belle. Yes.
DR. CRAWFORD: Stephanie Crawford. Yes. Joining Dr. Rizzo, I am from Chicago, yes, yes, yes.
DR. KRAMER: Judith Kramer. Yes.
DR. GARDNER: Jacqueline Gardner. Yes.
DR. LESAR: Timothy Lesar. Yes.
DR. NELSON: Louis Nelson. Yes.
DR. NGO: That's 24 yes, zero no's and

zero abstentions, for a total of 24 votes.

DR. GOLDSTEIN: Good. We got something done. Okay. So given that -- so then the sub-question that Dr. Rogawski had spoken of and Dr. Katz referred to, so given that, what guidance can we give the FDA in terms of additional studies that we think may be important or required for effectiveness or efficacy and what is the appropriate population? Open? Additional studies?

Oh, come on guys. There can't be any shrinking violets here.

Dr. Snodgrass?

DR. SNODGRASS: Oh, I tried some of this. The kinds of things that come to my mind are the frequency of testing for the eye exam. That's one issue. The sensitivity of that testing, so what kind of studies are needed, just look at what is the frequency needed, but also the sensitivity.

What kinds of techniques -- we've heard some of the limitations of the

techniques mentioned. Is there a functional MRI of the eye? Is there a pet (inaudible)? These are very expensive kinds of things, but there needs to be some studies that get at the sensitivity issue. I'm very concerned about -- you're missing the mile -- you're missing the early onset.

I mean, Genoray studies can be done. Who is more susceptible here? What are the genetic markers? Also, maybe there are data to be presented, but I haven't seen it is what are the studies of the mechanism of this toxicity? So what you are doing -- mechanism of action -- is you're flooding the brain with more GABA -- that's an inhibitory fact; that's just you're generally shutting down these abnormal seizures so that's fine, but as far as the eye is concerned, is there some specific mechanism that would lead to some other additional therapy that could semi selectively block that adverse effect.

And then the follow-up issue, if you're on or you're been on for three or six months and then are off, what's going to be the follow-up of those patients to look at the progression issue? And I think the other issue is, how many years of therapy -- I've heard one testimony about 15 years. Most of the data is shorter term, so we need data on longer term effect.

DR. GOLDSTEIN: So most of your thoughts are excellent. We're going to sort of like hold them a little bit on the side, because that gets to the toxicity issues that we'll be talking about -- that we'll be talking about later.

I think what we're trying to get at here is in terms of the patient population selection and also more data about effectiveness. As you rightly point out, I believe the studies were limited to several months of follow-up in general, at least in the comparative arm, are longer efficacy

studies required? What about the issue of refractory patients? What constitutes refractory in 2009 is not what was refractory when these studies upon which we're basing the efficacy data were done.

Dr. Katz? Anything else?

DR. KATZ: Yeah, can I make a suggestion about the order of things? We -- the first set of questions we asked in our questions that had to do with the visual field defect, and did we know enough about it, can we monitor for it -- I think the answer to these questions as to how much efficacy data we need is truly refractory.

This sort of thing -- those become pertinent once we've decided what we think the risk is. So I think looking back on it, we probably had a reason for putting those visual defect questions first. I think we can't really think about how refractory the patients need to be from an efficacy point of view until we have a sense of what the risk

is.

So I think I would suggest that we have the discussion about the risk and then once we get a sense of what the Committee thinks about how dangerous it is, I think that will inform the decision about how much additional efficacy data, if any, would be necessary. So I would I guess sort of lobby for discussing question one first, at this point.

DR. GOLDSTEIN: Obviously, we're here for your service, so we'll -- I guess we can do that, but maybe just a couple more minutes about this first, and then we'll switch back and then we can come back to this again.

They are -- they're clearly linked. All of this is linked but I think we're hopefully on a little train of thought, I just want to see if we can bring this to closure then we'll go right -- then that's going to, I think, be the bulk of the discussion after this.

So it's from the epileptologists -- refractory? Any other effectiveness studies?

DR. CHUGANI: Yeah, I think Dr. Mattson, who made a comment earlier on, hit it right on the head, that this would probably be in the refractory epilepsy patient and probably would not be number three or number four in terms of medication, but it could be numbers six, seven, or eight.

Now, the exception I could think of would be the patient with tubular sclerosis, where it seems to be a very good medication for that group of patients, not just what we're going to hear about tomorrow -- infantile spasms -- but for other types of seizures within that particular population.

So I think for me, tubular scleroses, it would be higher in the pecking order; whereas, the refractory complex partial seizure patients who would be maybe

six, seven or eight.

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: I'd just like to ask a clarification from FDA, because this question whether additional effective efficacy studies is required gets down to what's the basis for approval -- seems to me that the data presented clearly shows that this drug is efficacious compared to placebo, and the question is, by adopting this recommendation that it be in refractory patients, which parallels what was done in other countries, does that then require direct comparative effectiveness -- in other words, a study where you actually take patients who have failed other things and showing that this has additional efficacy?

DR. KATZ: That's one of the questions we're asking you. Seriously, one could look at it this way that the toxicity is so -- let me back up. Certainly, there are times, numerous occasions, in which we've indicated -- approved the drug, as indicated as second-line

therapy -- try other things first, and then when those fail, use this, without any evidence that that particular treatment actually works in those patients who've failed.

We do that invariably when we do it, because there's some toxicity associated with that drug, that if it doesn't exist in the other members of that class, so we say, save this to the end or close to the end. We don't usually require direct comparative data, but sometimes if the judgment is that there's a -- that the toxicity associated with that treatment is so severe that you wouldn't approve it unless you actually did have comparative data and show that this drug is better than other drugs, or alternatively that in fact the patients who were studied and the studies truly were refractory by some systematic definition that we knew about, the toxicity would be so severe that you wouldn't approve it until you had that sort of evidence.

It's pretty rare that we do that, but that's what we're asking here. We're asking, is the evidence of toxicity so significant that we really want to have comparative data and show that this works when other drugs work or that we'd want to have studies in which patients were truly refractory by some definition.

That's the question we're asking.

DR. CHUGANI: The reason I'm posing it back to you is if I'm not mistaken, Tysabri, when it was just recently approved for Crohn's disease, has a fatal side effect, and it was approved in a population that it was never studied in in terms of this whole issue about -- you know, they have to be refractory, et cetera, et cetera. I don't remember the details of exactly how it was worded, and so I'm asking the question about the precedent the FDA has set and whether -- you know, here, we're dealing with a side effect that some of the patients who feel very desperate don't consider

to be of the same order of magnitude as their underlying disease, and yet several of the epileptologists think that it's really severe.

So how do you sort that out if the FDA has varying approaches for different categories of drugs?

DR. KATZ: Yeah, I'm sure that's true. As I say, in the cases that I've been involved with, when we indicate a drug for second-line treatment, it's because there's some toxicity, but we don't think the toxicity is either so severe or so frequent that we have to have affirmative evidence that it's actually -- it actually works in those refractory patients.

Here, we're asking the question, because in some cases anyway the toxicity is severe, and globally, the toxicity is quite frequent. With Tysabri, the risk of PML was at the time of approval, one in a thousand or something, like at least it wasn't MS.

DR. CHUGANI: But it was frequently fatal?

DR. KATZ: Absolutely fatal, but quite rare. Here, this isn't fatal, but it's quite frequent. So that's why we're asking the question.

This is an unusual situation, and that's why we're asking whether or not you think that risk is so significant that we actually have to go and get additional data to prove either that it works in people who are truly refractory by some definition we understand, to how many drugs, yet to be determined, or whether or not it should be directly compared to another drug and show that it's superior.

Those are the questions we're asking because of the prevalence of this lesion and how frequent it is.

DR. GOLDSTEIN: Dr. Temple? You wanted to comment?

DR. TEMPLE: Yeah, we're confusing multiple things, all of which are interesting study design questions. For Tysabri, I think

the reason was that in cross-study comparisons, admittedly high-risk, Tysabri was overwhelmingly better than the alternative drug, so you knew it was going to be better. You know, it was almost two to one in terms of response, but you can argue about whether that was convincing.

Strictly speaking, to show that something works in refractory patients, there's only one vigorous way to do that: you take the drug that people are refractory to, and you randomize people to the new drug and to the refractory drug, and we have, as Rusty says, only asked for that in a few cases. That's sort of what was done with clozapine because the rate was 1.5 percent, and it was thought there needs to be absolutely clear evidence that it works in people who were refracted to another drug, and the only way to do that is to show that it works better than the drug they supposedly failed on.

There's a calcium channel blocker for angina where we made them do the same

thing. You had to fail on Diltiazime (?) and then show that this drug worked better than Diltiazime in those people. We also did that for the initial approval of captopril, where the drug was tested in people who failed on best available anti-hypertensive therapy, they were then randomized back to that therapy and to captopril and captopril was way better.

The reason you have to do that is people don't respond the same way by history as they do in a trial. And in the captopril trial, for example, 20 percent of the people who were refractory to the best available therapy responded to it when they were put into a trial, and I have a more recent example. You probably know about the fuss on COX-2 selective anti-inflammatory drugs. Every rheumatologist in the world believes that people respond differentially to these drugs, so you need a lot of drugs to be available.

At a meeting on this what I suggested was the way to prove that is take people who are refractory to some drug, randomize them back to that drug or the new drug you think is wonderful. Merck in fact did that. They took people who failed on Celebrex, no good response, and randomized them to Vioxx and Celebrex. I mean, it's a set-up for showing that you're better in a particular identified population. It's an enriched population of failures.

There was in fact a nice response to both drugs. They both did very well. There was not a dime's worth of difference between the two drugs. The idea that there was some individualization or that it worked in refractory people, that was wrong. It was wrong.

What you have here is persuasive anecdotes, perhaps, that it worked in people who failed on everything, but you don't have real proof. And one question for you all is,

do you need that real proof or is the story that they failed on four drugs and now they did great persuasive enough by itself? And that's sort of an expert judgment, but strictly speaking, it has not been proved.

DR. GOLDSTEIN: Thank you. I have three or four more comments, then we'll preliminarily close this part of the discussion. We'll come back to it again later after we deal -- talk more about the toxicity portion.

Dr. Vega?

DR. VEGA: One of the -- in terms of the patient populations, as I was reading before I came to the meeting, some of the literature -- and I didn't see in the presentations here, is in terms -- we have a very diverse demographic population in this country, and I have no clear picture of who these patients who had participated in these trials are besides that they have a condition.

I am not sure they were, for the most part Caucasians or they were also

African-Americans, Hispanics -- I would now want to see a widening in terms of the disparity gap, in terms of who gets to use this medication, so I do believe then I would want to see more evidence in terms of different subgroups in these trials.

For me, this is an ethical question, because I can't imagine people having to decide to go to another country to get a medication just because they wanted to. I believe -- I am someone who believes a lot in -- I do a lot in community based participatory research so the testimony of people is tremendously important to me.

I get great comfort in knowing this -- this is not a brand-new medication. It's a medication that's be used in many other countries. So I think then, yes, we don't have all the evidence that we want to, but from things then -- for some of the people that have spoken in the public and some of the testimonies that we got

previously, the quality of life for these children and adults is worse than what happens to their vision if they don't get the medication, so I see this as an ethical issue where I think if I -- versus having a good quality of life, and people who are blind, I mean, they can live a good quality of life. But again, I would want to see more diversity in these studies.

DR. GOLDSTEIN: Thank you.

Dr. Nelson?

DR. NELSON: Well, I guess I have a comment and a question. Maybe Dr. Temple could kind of reflect on this because this was just a thought I had while he was speaking. But -- you know, one of the differences between Vioxx, Celebrex, and this disease is a little bit of the objectiveness of the findings.

You know, pain and discomfort versus a seizure, I think, makes the data a little bit different. And the other difference, I think, between this drug and

those are the presence of a registry, assuming those go forward the way it's supposed to.

So is there the potential in terms of collecting prospective type of data? The ability to use a registry, to kind of catalogue responses to this drug compared to previous drugs? So it would be somewhat of a retrospective data collection but -- you know, if you've got a sense as you went forward for all these people who were refractory to other medications through their registry and what medications they had failed, and then their new clinical status based on prospective data collection, would that provide any sort of helpful comparison of the two datasets?

DR. TEMPLE: This is something that comes up all the time. People who are interested in comparative data always hope that they can do it in some way other than controlled trials. I usually take the position that you

can't, and I don't believe you can find persuasive evidence here -- after all, the situation's different -- they've signed up for this wonderful drug even though it's potentially toxic, maybe they're going to take it better than the drugs they took before. It would be very hard to make persuasive data that way.

We do think the registry has a lot of promise for toxicity, however.

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: Just to follow-up briefly. I certainly agree with Bob about what kind of data you can get from a registry, but also just to say that we have to decide -- and again, with your help here -- what's the evidence necessary to approve the drug. We have to conclude that it's safe and effective before we approve it. We can't push that part of the question off into the post-marketing. We actually have to decide whether or not it's safe and effective before we can approve it. So a registry that got us data that we thought was critical to our assessment

of either safety or effectiveness, really doesn't help us make the initial decision about approvability.

DR. NELSON: Well, if I could just answer -- or follow up with that. I'm working on the assumption that the efficacy question is relatively moot, because I think we've decided that it's effective. So now the question really is, do we need more data to prove that it's more effective than other things. And I mean, I totally agree that if you could do a prospective study the way you've already described it, that's great, but that takes years, and the anecdotes are persuasive and the data seems to be real that the drug has benefit.

I think the question we have to answer is -- the toxicity question, of course, but if the question is, is it more beneficial than other therapies, would this additional data be worth having? I'm not saying we should approve it based on no data and just hope the registry works, but would

this be additional data that would be helpful?

DR. KATZ: Again, just address that, we're asking the question, what sort of data do we have to have in order to approve it. I mean, that's the -- there's always lots more data you could get on a drug that is not necessary for the decision about approving it. We're asking here specifically what sort of data do you think we need to have so that we can approve it.

DR. TEMPLE: One answer might be, and I think it's the answer that was being given -- I need to know that it's effective and I need to have some kind of evidence which could include some of these persuasive stories to think that it might offer something special, and somebody could conclude -- the Committee could conclude -- that that is enough even though they don't have the kind of studies I want to prove that it works in the refractory people.

DR. KATZ: Of course. But all I'm saying is, the question we're asking is, what is

the minimum data packet that we need to have in order to be able to decide that we can approve it, whatever that turns out to be.

DR. GOLDSTEIN: Just so that the folks who had their hands up don't get too upset with me, what I do again is I let the Committee members who haven't asked a question at all, first as questions, then we go through and we let people ask a second question if they've already done so. So again, what I'd like to try to do is bring this part to at least a preliminary conclusion, with the next -- I guess we have four or five folks to speak and then we'll come back to it again later.

Dr. Mizrahi?

DR. MIZRAHI: I wanted to speak to Dr. Temple's point about the issues related to intractability, and so while I would be very happy to have different kinds of studies really focusing on intractability and be certain about exactly how this drug compares to others, I really don't think that that's something that we

could realistically say that we could do, and from a clinical point of view, I'd say that it'd be interesting but it really wouldn't be the clinical issue for me, that I think intractability is a sort of concept that you can't define but you know when you're there. And unfortunately, that, I think, is really sort of the state of what epileptology is in a lot of ways.

So I think the issue for me is not a matter of -- is not a matter of quantifying the intractability and then the efficacy, it's a matter of accepting the efficacy of the drug with the data that we have and then somehow quantifying the risk so that then intelligent decisions can be made. And I'd try to leave it that way and shift back to Dr. Katz's point of view of getting a better handle on the risk.

DR. TEMPLE: I don't want to be misunderstood. I in no way suggest that's not a reasonable position to take. I'm merely -- I'm

no design maven or freak or something, and strictly speaking, they have not shown effectiveness in a refractory population in a rigorous way that we would accept. They have some evidence that it does work in a refractory population that may be convincing enough, in fact, some of the anecdotes are pretty convincing that we heard in the public session, but that's not the same as a trial in which you randomize people back to the drug they failed on and the new drug. That's all.

DR. MIZRAHI: A quick follow-up to that. We have these -- in some ways, we've had the same conversation about epilepsy surgery where we talk about intractability, we talk about the procedure really working, but then somebody says, show me the randomized, double blind trial and we don't have that. So it's pretty analogous in some ways.

DR. GOLDSTEIN: Dr. Twyman?

DR. TWYMAN: Dr. Temple, I'd just like to challenge you on that just a little bit,

because the two pivotal studies were actually -- had prospective baselines in which they had 12 weeks of exposure to their baseline drug which were poorly stabilized over that 12-week period and then studied for 12 weeks in a randomized fashion after that. And so technically, that is data which they had controlled with regard to their degree of refractiveness to those current therapies at that point.

DR. TEMPLE: It's not a concurrent control. The captive rule study I just described did exactly the same thing, and during the randomized blinded part of the study, something like 20 percent of the population that was completely refractory to the standard therapy responded to it. The conditions change. That's why you have a randomized parallel.

DR. TWYMAN: But by definition, this was adequate data for adjunct of therapy in a patient population status refractory.

DR. TEMPLE: No, it proved that the

drug worked better than -- well, a high dose worked better than a low dose. I don't dispute that at all.

DR. TWYMAN: Right.

DR. TEMPLE: You don't know what would have happened if in the controlled part of the study they'd been randomized back to the treatment they supposedly failed on. They weren't on it anymore or some were, but not all of them. That's all.

DR. GOLDSTEIN: Dr. Rogawski?

DR. ROGAWSKI: So what I'm struggling with is this issue that there might be a patient here or there that would have an unusually positive response to this drug, and this is of course a very difficult in any controlled trial situation to define. However, we do, I think, have some information about whether vigabatrin specifically is any better or worse than other anti-epileptic agents in refractory patient populations.

For example, Mark Brody, in 1999,

before a lot of the safety issues were front and center, published a controlled trial in epilepsy research with 100 patients who were refractory to carbamazepine who were randomized in a double dummy blind fashion to vigabatrin, and another about 100 to Valpro, and what he found is that the addition of both of these agents increased the response of the patients -- 53 percent of the vigabatrin patients and 51 percent of the Valpro responded, and in fact 17 percent of the vigabatrin patients became seizure-free and 19 percent of the Valpro patients became seizure-free.

So the conclusion there was that adding on a non-sodium channel blocking drug to carbamazepine can produce an increment in benefit. The problem, though, then is that's not telling us that vigabatrin is any better than Valpro or any of the other drugs that we have available and now that we understand the significant risk of vigabatrin, that concern,

I think, becomes an issue, and so for me, doing further studies like this, either in a Phase IV kind of a setting or preregistration, I think is very important for us to understand in what population in patients the drug is going to be useful for.

DR. GOLDSTEIN: Dr. Sleath?

DR. SLEATH: My question is actually related to vision loss, so do you want to wait?

DR. GOLDSTEIN: Yeah, let's hold off on that. Dr. Weinstein? He abstains.

Dr. Chugani?

DR. CHUGANI: I just have one more comment. I just wanted to remind the Committee that vigabatrin -- as a pediatric epileptologist, vigabatrin seems to be different from many other anti-convulsants. How many anti-convulsants do you know that have such a striking efficacy for infantile spasms? Most anti-convulsants don't work.

You've got ACTH, you've got vigabatrin. So that immediately sets this

drug apart from many of the other anti-convulsants, and the same thing for the issue of tubular sclerosis. Why should it have such a very strong efficacy in patients with TS? These two points tell me that this is a very different medication.

If the Committee then demands -- the FDA demands a trial against a lot of other anti-convulsants, I'm not sure you're going to capture the uniqueness of vigabatrin. Even in patients with complex partial seizures who are intractable, over the years, I've been surprised at the ones who have responded to it. I don't understand why it should work on some patients.

One of the anecdotes about the traumatic brain injury, I have two patients like that as well -- shaken baby syndrome, head trauma -- and somehow vigabatrin works well for them when nothing else works. So there's an element that we don't understand about the uniqueness in certain populations.

We do understand the spasm population and the TSC population, but the complex partial seizures -- and if you wanted a trial against-- you know, kepera or Lemetor (?) or whatever, I'm not sure you're going to bring -- you won't capture that. And that's my concern.

DR. GOLDSTEIN: Well, let's bring this preliminary part of this section of the discussion to a close.

Just to summarize, I think the things that we've discussed are how you would operationally define a refractory population, but epileptologists deal with this now, certainly in terms of deciding on surgery or not or switching drugs. Whether that could be addressed or should be addressed in a trial before approval or after or can't be done, I think we can hold that in abeyance for the time being and maybe come back to that again a little bit later.

What I'd like to do now is switch

over to what a major portion of the discussion was this morning, and that's the toxicity. We had two major issues that were discussed. One was the IME problem, and the thing that dominated the discussion was the visual issues. As we discuss this, I just want to remind the Committee that infantile spasms are something that we're going to be discussing tomorrow. I know it will creep in from time to time, but the real focus here has to be partial complex seizures. We have an entire meeting tomorrow on infantile spasms.

So as we start talking about the visual problems, again, I want to take advantage of the expertise of the Committee. There are a lot of technical issues that were discussed this morning related to how one measures visual deficits, how reliable that is, how valid these various measures are, how practical it can be done, whose doing them, and like issues, so as we start this section,

I'd like the ophthalmologists to have a chance to comment first.

And the questions -- why don't you put up the questions? So these are the formal questions -- the formal questions are what's listed as question one, and at the same time, part of it is actually Question 6. So Question 1, the primary question is, vigabatrin has been shown to cause irreversible visual loss, central -- question central and/or peripheral. And then there are the several sub-questions there.

And then Question 6 that's linked to it, is additional data related to the visual loss -- should that be obtained before approval? So again, I think these are sort of linked issues. We already had a comment from Dr. Snodgrass earlier about some issues that he thought were pertinent for the visual deficits.

So first, our ophthalmologists. Technical issues? Things that you've heard

from this morning that you'd like to comment on?

Dr. Heckert?

DR. HECKERT: I would say certainly -- you know, you just had this question, does it show that -- clinically meaningful vision loss -- does it occur? I think everybody agrees that it certainly occurs. I do think that in anybody who can perform a visual field, that that is by far the best test to try and quantitate this.

I think the OCT is intriguing, but I'm not sure there's much -- well, I guess some of this gets to infantile spasms -- there's not normative data for children, but also, I think there's still a lot that has to be learned about that before it becomes a truly useful screening exam.

As far as ERGs, I'd say that is probably the least available of all testing and also I think it's the hardest to standardize. I think some people have to

travel quite -- at least where I live -- they have to travel three hours to get an ERG and the population I serve -- I serve people from the Upper Peninsula in Michigan, and if they have Michigan Medical Assistance, they have to go to Ann Arbor, and that's more like a nine-hour drive. So that is not in any way, unless you're in a major urban area, a widely available test.

DR. GOLDSTEIN: Dr. West?

DR. WEST: Hi, Connie West, ophthalmology, Cincinnati Children's. I think that yes, I would say that it -- the continued treatment could result in a clinically meaningful loss of vision in some patients. I think there's a subsequent question of would it -- would continuing the therapy, though, be better than the risk of visual loss? Visual loss, although it's certainly a significant event in one's life, it's not the end of one's life. As seizures could cause the loss of life, blindness in and of itself does not.

The thing that I noticed that was absent during this was although we were talking about ophthalmologic exams, I don't think that we have specified whether these examinations of the visual systems are being performed by ophthalmologists and optometrists.

I think it's a very important distinction, as somebody down the table brought up earlier. For those of you who don't know, there are opticians who make glasses, there are optometrists who diagnose and treat some mild visual conditions, but then there are ophthalmologists who are medical and surgical doctors who treat visual abnormalities, and I think that just as it's being considered that a board-certified neurologist would initiate the treatment, I think that you need to have specifications for what sort of qualifications the practitioner following the potential visual changes would have.

I don't think that although they talked about monitoring visual fields, it wasn't specified in the material that was presented what constitutes a significant change in visual field because there is variability from testing from day to day and time to time.

Is it a loss of a certain number of degrees or not? It's also not specified what sort of equipment would be used to do it, for instance for peripheral visual field loss, the automated perimeters do not go out that far -- do not go out to the initial 90 to 85 degrees out there where you're going to see the loss occur first, so that would have to be with a Goldman perimeter.

And so I think that those are the major issues. I also would agree with the ERGs. If somebody can't perform -- today, we're talking about adults, of course, with CPS, but if an adult cannot perform a standard perimetry test, whether it's an

automated -- whether it's a static or dynamic visual field test -- if they can't perform a visual field test, I would wager that it's unlikely that they would be able to complete a non-sedated ERG having personally performed ERGs myself.

What that means is the patient has their eyes dilated, they're dark adapted for half an hour, their corneas are numbed, and then a contact lens is inserted into both eyes at the same time, they're positioned supine on a table, they have to sit with their face under a bowl and then have bright lights shone into their eyes while the recordings are made. They have to not blink the contact lenses out of their eyes, and they have to be able to participated with the whole thing.

And so even though 20 percent of people can't do the visual field test, I think that that's probably -- a lot of those patients would not be able to do ERGs and

plus they're not widely available, they're not reimbursed well, so people won't be -- I think even as time goes forward, you're going to find less and less centers doing ERGs. We won't even do them now on adults because we lose money every time we do it. Every time you put a patient in the Chair, you lose money.

DR. GOLDSTEIN: Dr. Heckert?

DR. HECKERT: One other thing about that, and it has to do with just the stimulus is a bright flash -- which you flash frequently which may not be advisable in epilepsy.

DR. GOLDSTEIN: It's repeated flashes, but -- okay, so let's look at some of the sub-questions with that background. Does the Committee believe that continued treatment results in a clinically meaningful loss of vision in some patients?

I think we can -- let's try a show of hands first. I think we've spent a lot of time discussing the data behind this. Does

the Committee feel that continued treatment results in a clinically meaningful loss of vision in some patients? Okay, I think we can dispense with that one. I think the answer was a relatively uniform yes to that.

So has the sponsor shown that this visual loss can be detected before it becomes clinically meaningful? This is a much more difficult question, because as we went over this morning, the longitudinal follow-up data on individuals is not extraordinarily strong. We saw the data on individual patients that the FDA showed where we've got some going down, some going up, so it's -- let's open this to discussion.

Has the sponsor shown that this visual loss can be detected before it becomes clinically meaningful?

Dr. Jensen?

DR. JENSEN: So a couple of things. One is, is it fair also to ask at the same time -- is it equally as valuable to

say -- has -- is it -- does it appear that the visual loss could be detected prior to it becoming severe versus has the sponsor shown that? I get -- I mean, for operationally, in terms of thinking about moving forward the drug, do you want us to answer both of those questions or just has the sponsor shown?

DR. GOLDSTEIN: The question was, has the sponsor shown, but again, the purpose of this exercise isn't to take formal votes on each one of these issues; the purpose is the discussion to hopefully inform the FDA of what our feelings or what our opinions are.

DR. JENSEN: Because it does appear that there is some evidence that theoretically you could pick up early changes prior to that becoming severe or impairing the function, but I guess there's some debate as to whether the studies that had been shown to us achieve that aim.

DR. GOLDSTEIN: Dr. Sleath?

DR. SLEATH: I just had a clarifying

question related to this from this morning.

Dr. Farkas, you talked about that you thought study 03 was important, more important than the company did, and the study was stopped and I never quite understood why it was stopped. It stopped with only 25 subjects out of 200, and I wonder if that was because of safety reasons. And then Dr. Sagar in his slide 18 talked about a pooled cohort analysis that said the FDA reviewer had a problem with, and is that different from study 03 or the same? Because to me, I need to understand that.

DR. FARKAS: I think that -- there were several studies started by previous sponsors, and I don't think FDA is certain as to why they were stopped, but it was not because of safety reasons, and it seemed from the information that we had that it was somewhat more organizational reasons, I suppose. Then the question about -- there were two studies that --

DR. SLEATH: Can I ask -- how do you know it wasn't safety?

DR. FARKAS: We can direct it to (inaudible). Is that okay with you?

DR. CUNNIFF: Sure.

DR. FARKAS: Go ahead.

DR. CUNNIFF: Study R003, after the discovery of the peripheral visual defect after about eight years of marketing in Europe, Europeans Medicine Agency actually required 12 preclinical studies and 5 different clinical studies.

One of the risk management tools employed by Europe -- and which we're employing today is because of the side effect we've limited the indication to a very, very narrow patient population. So study R003 was required by the Europeans Medicine Agency, but because the patient population in Europe had been narrowed down to a very restricted resistant complex partial seizures in the infantile spasms, that study did not enroll.

So Aventis, after a few years of trying to enroll that study across the European continent, went to the EMEA and they got agreement that they could -- would not be feasible to enroll this study so the European Agency agreed it could be terminated. So it was not a safety issue, it was just the number of patients available weren't out there.

DR. GOLDSTEIN: Thank you.

Dr. Weinstein?

DR. WEINSTEIN: Two points. Having had multiple visual fields over the last couple of months, it's tough. And I've got to tell you, when they put the little contact in my eye to do ERGs, that's even tougher. But putting that aside, I'm naturally paranoid, and I guess I'm paranoid because I heard that the OCT looks at central fields -- if I heard that correctly and if I've heard that correctly, that was being offered as to look at peripheral vision, and if we're seeing changes centrally, what the heck is

going on out in the periphery and is this a more global retinal abnormality?

DR. GOLDSTEIN: Dr. West, did you want to comment?

DR. WEST: I think -- I'm not an expert on OCT, but OCT is measuring thickness of various layers of the retina, and you can use the nerve fiber layer thickness around the optic nerve head, also known as the peripapillary area, and a decrease in thickness of the nerve fiber layer could be used as a proxy for loss of retinal function in the periphery, which would then be used as a proxy for visual field deficit. So you could use it.

It's a -- it's used as a proxy for it. It's an end -- it's a side effect of it you would have. If you've lost visual function peripherally, you may have also lost nerve fiber layer thickness in the peripapillary area which is where the OCT can measure the various perimeters.

DR. WEINSTEIN: Does that mean that

you have to have the peripheral loss first before you lose it centrally, and how much does it imply that the deficit peripherally is more severe?

DR. HECKERT: If I could say one thing about that. I think the promise of OCT has to do with -- you have to lose a lot of retinal function before a visual field becomes positive, so at least theoretically in time, it may end up being more sensitive.

DR. SERGOTT: Could I make a comment about this? So the real promise of OCT has been stated is that it was first studied with glaucoma and then diabetic retinopathy and the statement is in actually glaucoma, the changes to OCT precede field loss. I mean, this is a patient with optic neuritis and multiple sclerosis, and actually, this patient has a normal visual field, and what you can see is that here's the circle around the optic nerve and as Dr. Chambers correctly said, we do study the macula and that's only central vision, and

when Dr. Wild studied that with the vigabatrin that was normal.

But we also studied the area around the optic nerve, which then includes all the fibers, all the fibers in the retina, not just the macula. Because here's the macula over here, all these fibers are coming in here. So in glaucoma as well as other intrinsic diseases of the optic nerve, structural change appears to precede field change.

Now, it's interesting that in extrinsic lesions of the visual system, that is the chiasm, work proposed to one of our former fellows in New Zealand shows that the field precedes OCT changes if we're compressing the chiasm or the optic nerve with a mass lesion, but in intrinsic lesions, this change does precede field change.

OCT, there are now many billing codes for this and Medicare and other insurance companies recognize its value as a

precursor to field change.

So here, we have a patient who actually recovered from an optic neuritis but is left with structural axonal loss. So in fact, it is more sensitive than field. And I think everyone is correct, it has great promise, we have a little bit of cross-sectional data from Dr. Wild, but coupling this -- and again, addressing those patients that we have to be worried about, that is those outliers, could this give us a signal that maybe we could have the patients monitored in a way that would maybe just help them and help the clinicians in this regard.

DR. GOLDSTEIN: Thank you. So let's try to deal with this -- I'm sorry, Dr. Chambers. I'm sorry. Missed you.

DR. CHAMBERS: The direct promise for OCT is to measure the thickness out in the periphery. That's what we're saying that OCT has not currently been validated to do. So you can measure the macula and measure the thickness

and that has tremendous promise and you can see the different levels. You can look around the optic nerve and that's downstream from what the periphery is and depending on the location around the never, you can predict some particular areas if it's gotten down that far, but if you just start losing peripheral fields, you may not yet see it at the nerve and so that's the issue that you can potentially lose some of the periphery without having yet it being picked up around the nerve.

DR. GOLDSTEIN: Dr. Gardner?

DR. GARDNER: I'd like to ask Dr. West, who talked about who can conduct tests and thinking again about accessibility, did you suggest that optometrists could suitably do the kind of monitoring that's being discussed or possibly recommended?

Ophthalmologists, not being everywhere, I would expect opticians -- could optometrists be doing this or not?

DR. WEST: To start with the opticians

first, opticians are sometimes licensed in states, sometimes they can dispense glasses without a license, so opticians would be completely off the table although they can fit contact lenses in some states.

Optometrists, I think that there are some very good optometrists out there who could, individually, interpret visual fields but I don't think that as a generality most optometrists would have the training and decision-making abilities to interpret complex visual field changes in a patient with a complex medical disorder like complex partial seizures.

It's not to say -- and it's not to say that all ophthalmologists would be good at doing it either, just like not all neurologists would be really good at prescribing medications for seizures, but I think you would have a better chance of getting somebody qualified to interpret those by having an ophthalmologist do it.

DR. GOLDSTEIN: Let's see if we can deal with letter B, has the sponsor shown that this visual loss can be detected before it becomes clinically meaningful? And I guess another way of stating that, could the visual loss occur in the absence of just be found before it was mild? Though we did have data that was -- at least some data that was presented about that, but the formal question is, has the sponsor shown that the visual loss can be detected before it becomes clinically meaningful?

DR. WEST: May I ask a clarifying question?

DR. GOLDSTEIN: Sure.

DR. WEST: When you say this, do you mean -- I mean, it can be, occasionally, but not is it routinely detected before it becomes -- which are you asking? Can it be? Yes. Is it routinely?

DR. GOLDSTEIN: I think what we would be thinking of -- and Dr. Katz, you can correct

me if I'm wrong -- but in general clinical practice, if we were following a series of people that were on this drug, would we expect there to be close to most, if not all, detected before the visual defect became clinically meaningful or are the data insufficient to answer the question.

Dr. Katz, you wanted to clarify?

DR. KATZ: I think that's basically it. We want to know whether or not there's a way that we can reliably pick this up before it matters to the patient if there's a way to do that.

DR. GOLDSTEIN: Universally?

DR. KATZ: No, reliably -- by reliably -- universally, it would be great, of course. We don't expect that. But most of the time, routinely -- we expect of certain screening lab tests all across medicine, to be good at what they purport to do. So that doesn't mean you pick up 100 percent of everything that's abnormal, but you expect it to

perform reasonably well. You expect most patients, if they have a deficit, to be picked up. So it's reliably, or whatever word you want to use, mostly, not in 100 percent of cases although that would be nice.

DR. GOLDSTEIN: Okay. Dr. Chugani?

DR. CHUGANI: Can we do a show of hands now?

DR. GOLDSTEIN: Could we -- well, let's see, I actually have two more comments first and then I guess we'll try to deal with it.

Dr. Rizzo?

DR. RIZZO: I think I'll wait.

DR. GOLDSTEIN: Sounds good.

Dr. Heckert?

DR. HECKERT: Well, I was going to ask, do we have to answer that question based on the data that was presented to us or about our beliefs about testing. Because it seemed that a lot of the tests -- I remember one of them, they had this summary where some people only had one

field and some people had maybe three fields, and this would be a condition where you would be doing fields frequently for years. And I think if you did that, more than likely, you would capture most people as soon as the defect became significant. And of course, as soon as you got a really suspicious field, you'd bring them back sooner than your usual -- you know, their routine, because you want to see if that's real or not. So I think that if somebody is followed rigorously with it -- based on the data we've got, it's just experience in managing people with visual fields -- if you do them frequently, you can catch these things at an earlier phase.

DR. GOLDSTEIN: So I guess the way to think about it is that in general clinical practice, in patients that are being followed with serial visual field, given the data that we saw, would you expect to detect the visual field detect before it became clinically meaningful.

Dr. Snodgrass, one more?

Presuming that you could do an

adequate test on the patient to begin with. If you couldn't do an adequate test on the patient to begin with, then there's nothing to follow.

DR. SNODGRASS: (inaudible)

DR. GOLDSTEIN: This is adults.

Dr. Kramer?

DR. KRAMER: Just a clarifying question. It seems to me that the way the question is worded is asking whether the sponsor is shown with what they've done and what they're recommending be the basis for following these patients whether or not in general they have proven that they will detect these things before they're clinically meaningful, not whether in general practice we theoretically could.

I'm just having a hard time understanding how we're --

DR. WEST: That was my original question also.

DR. GOLDSTEIN: And I think Dr. Katz tried to formulate in a way that -- to put it in

the perspective of, given the data that was presented, would we -- do you think that most visual field defects would be picked up before they were clinically meaningful based on the data that's available.

SPEAKER: And what's being recommended is --

DR. TEMPLE: That's not the way -- even if it's not the way they did it. Can you think of a way that it could be done?

DR. KATZ: Is there a way -- forget for the moment -- it's true, the question says, has the sponsor shown. It's because we're trying to get at sort of an evidence-based answer. But in the opinion of experts, obviously we have some at the table, is that given what we know and don't know about the natural history of this lesion -- that we have to accept on face because that's the data that we have with regard to the lesion itself -- is there a way to pick this up, reliably, in most patients, before it gets to be clinically

meaningful?

And I think the answer to that question includes not only is there a test that can do that, but also is there some reasonable frequency of employing that test that would -- that's practical, that can be achieved?

And with regard to the first question -- the first part of that question, which is is there a test or tests that can do it, I think we need to have a little bit more discussion about how reliably can this test be done, particularly in an epilepsy population if there's any evidence about that. But -- you know, we've heard, well, 20 percent of people can't give you a good visual field and there's nothing you can do about that.

Well, what we have to think about is not being able to follow 20 percent of these patients. And I'm not sure that's in an epilepsy population. That's probably the

general population. But is there some percentage that -- on whom we cannot do the tests adequately that becomes a problem. Suppose we couldn't do it in 50 percent? Does that sort of give us a big problem? But we've heard 20 percent.

I'd like to have a little more discussion about can -- all aspects of that question. Is there a test, a test that if you could do it would be reliable? How frequent would you have to do it? But also, really, in how many people can you do it reliably?

DR. GOLDSTEIN: You're the experts.

DR. RIZZO: Regarding what's been done and what might be done, there are a couple of tests that are simple to administer and very useful information-wise about central vision such as spatial contrast sensitivity which was not reported on but which is used ubiquitously in situations like the one we're discussing today.

We've heard no data. We've only heard data on visual acuity.

DR. SERGOTT: That's correct, because there is no data about that that I'm aware of. Maybe Dr. Farkas is aware of some contrast sensitivity data, but I am not.

I think the other issue about, can this test detect this, it's the same test that we use to detect glaucoma in this country, so if you say it cannot be detected, then we cannot detect glaucoma. However, we're very effective at detecting glaucoma at an early stage and the data about -- it's 20 percent of specifically epilepsy patients from Dr. Harding's study published in Neurology, I believe in the year 2000. Now, the work that I cited, a joint study from Toronto and Detroit, showed that in glaucoma patients 24 to 33 percent could not perform a field.

And we still take care of those glaucoma patients the best we can if they

can't do a field. So I think we can address that, and maybe not perfectly.

And I think we have -- as we go through this discussion, we don't have all the precise data that the Committee, the sponsor and the public would like to have, but we have very informative data about the nature of this test in ophthalmology, we can test peripheral field reliably. We've shown that over the years in glaucoma and I think that's the comparison to make.

DR. RIZZO: May I ask also about Critical Flickerfusion? It's a relatively inexpensive test. It doesn't require all of the paraphernalia that ERG does. It gives reliable information about temporal processing in the visual system. All we've talked about today has been spatial processing and temporal processing may also be important.

DR. SERGOTT: I think they are excellent points. This is Dr. Carol Westhall from Toronto Hospital for Sick Children, Ph.D.

scientist in electrophysiology, and I'll ask Carol to address the question about Flickerfusion.

DR. WESTHALL: I'm actually going to address the question about the contrast sensitivity which I measure in all the children, but this is tomorrow's, but there's also one case that's been brought up before about a 10 year old with epilepsy, and that child, she did have normal contrast sensitivity, normal visual acuity, normal color vision, normal ERG. She had a measure visual field defect.

Critical Fusion Frequency, I haven't actually done that.

DR. RIZZO: How about the useful field of view which depends on temporal processing, selective attention, and divided attention, and as a real world measure, in context of shrinking of the visual fields, even in the absence of sensory loss?

DR. SERGOTT: I think they are very valid measures that need to be done, but I'm not

aware of any data to date about that with this medication.

DR. RIZZO: Thanks.

DR. GOLDSTEIN: Dr. Nelson?

DR. NELSON: You know, Dr. Sergott, in your slide 11, you give a table that actually shows, I think maybe -- I guess, perhaps, your kind of concept of how these tests work, but I assume mild means preclinical or relatively preclinical, and it shows that these tests -- I assume plus/minus means it doesn't work very well. So that's why I had asked that question before about whether applying them in a serial fashion might actually give you better data, but this would suggest at least that these tests are not very reliable.

DR. SERGOTT: Well, I want to agree with you that a serial test in the visual fields, as I guess Dr. Farkas said and I also said, gets better results. So in these patients, as was said before, I think by our pediatric ophthalmologist -- the more the tests

are done, the better they're going to get. So the checkmarks were just a point in time, but if we would draw a line, we would see improvement in the quality of the field.

DR. NELSON: Right. I guess when I said serial, I guess I was mis-speaking semantically. I didn't necessarily mean one test over time. I meant if you performed kinetic perimetry right now and then that didn't show anything, so then you performed ERGs -- maybe that subpopulation who didn't perform well on the perimetry might actually have a finding on ERGs, and if they don't, maybe the OCTs would work, because it seems to me that what we've suggested is we just do one test and either they have it or they don't, but maybe the one test isn't right for any given patient, and the different tests performed back to back would maybe give you a better --

DR. SERGOTT: And that's exactly where I try to say -- and that's exactly how we teach our residents and fellows, that this is a

process, not a single event, and there will be patients who we can do the static field on, some with a kinetic -- but then as you said, we're going to have to go to other ways. And that's the practice of clinical medicine and clinical ophthalmology.

But if I were presented with patients from our very large seizure group with Michael Sperling, that's exactly what I would follow. Can they do it?

If they can't, I'm going to other means. And then have a discussion with Dr. Sperling so he could have a discussion with the family regarding the risk benefits. We can't get any visual data. What do we do? Or we can get visual data and we're getting a little signal. And again, we want to protect from getting to that very bad point. And I think we can get that signal, because we can get that signal usually with glaucoma.

DR. GOLDSTEIN: Dr. Weinstein?

DR. WEINSTEIN: My paranoia, again.

You know, you compare these tests of patients with glaucoma and that they pick up glaucoma. I presume the patients that you're doing this -- you're not doing this as a screen for glaucoma, but rather at some point where they've become symptomatic and you justify doing the test -- but the question is, is there a test that before they become symptomatic, that's easily doable in a large population that will identify who may need to go on and do this?

DR. SERGOTT: The visual field test. And you've had fields yourself -- and we usually don't let physicians perform fields, but that's for other -- maybe for cognitive reasons, but usually physicians are trying to figure out the test. But in all seriousness, you know what it's about, and you've probably gotten better with it as time has gone on. The field defects that we pick up with early glaucoma -- and I'll let Dr. Farkas and Dr. Chambers talk about this as well -- are smaller defects often than what vigabatrin has.

DR. WEINSTEIN: But they're smaller in the beginning. The question is, can you identify small lesions in patients on vigabatrin early on in the course by doing fields?

DR. SERGOTT: My answer is yes in some patients, but not in all patients.

DR. WEINSTEIN: And percentages? You want to guess?

DR. SERGOTT: No, I don't want to guess.

DR. GOLDSTEIN: Well, that's good.

Got to go in order. Dr. Chambers.

DR. CHAMBERS: And I don't want to guess on that answer, either. I just wanted to point out on the mild issue, the location for the static and the programs that are run for the static or the threshold, generally for glaucoma, it's a central 30 degrees. There are standardized programs. They're all well worked out, that go out to 60 degrees. What was in the table going out beyond 60 degrees, so what was being considered mild along here is outside of

60 degrees. And we don't have good programs to go outside 60 degrees except for a Goldman, and the Goldman would be a manual person going and doing it.

And then you need the same technician doing -- one, you need an experienced technician; and two, they need to be doing it -- the same person needs to be doing it along or the fields change.

DR. CHUGANI: Can I have the slide about the automated kinetic perimetry, please? We didn't show this slide earlier, because there is not yet data in vigabatrin patients with this, but the Octopus and the Humphrey Perimeters do have programs for automated kinetic perimetry, and these -- actually, the Social Security Administration -- it's not that one either -- has endorsed this, and again, as Dr. Farkas' briefing document pointed out correctly, without much clinical data, but there is an automated kinetic test available with these two machines.

In neuro-ophthalmology, we don't have a whole lot of experience with it but we are getting more. It actually uses a 3-4 isopter (?), it takes about three minutes per eye -- this is all that's on the slide -- and it measures points along the meridians. Again, it gives us another tool for some of those patients that we need to see. But that's -- there is automated kinetic perimetry now.

DR. GOLDSTEIN: Dr. Crawford?

DR. CRAWFORD: Thank you. I think one of the reasons so many of us are struggling with this question is that most of us can probably say it should be yes and no depending upon what qualifications we put on those questions in our mind. It's almost looking again at Dr. Farkas' slides on time to onset versus speed of progression.

I think what -- perhaps what would really help us in terms of if this drug is approved or what's needed or perhaps clinical

researchers going around the table, are there any epidemiological studies or other designs that would actually answer a question to perhaps examine what predictors would say which type of patients would more likely have fast versus slow progression to vision loss? Because the slow progressors, likely there are tests that can meaningfully detect vision loss, inadequate time, but those who are fast progressors, I don't know.

DR. GOLDSTEIN: Who -- Dr. Crawford, who are you directing the question to so that way -- just in general. Okay. Are there ophthalmologists?

DR. HECKERT: I don't think there's any test other than visual fields that help you predict that which goes back to the value of doing frequent fields. And that's the only way to get a slope of how quickly things are changing.

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: We actually didn't talk

to each other, but I have a question about the same slide, Dr. Farkas' slide 39. The trouble I'm having with this discussion, and I'm clearly not an ophthalmologist, but if in fact the defect that's caused by vigabatrin is a slowly progressive defect, that's a completely different situation than if it's an immediate fast fall off, and I may have misinterpreted Dr. Farkas' presentation, but I interpreted it to indicate that we -- there's not enough evidence to know which of two, not that both occur.

And in that case, I don't understand why we're really asking the ophthalmologists what tools they have to detect it, because if it's the fast falloff, it doesn't matter what your tools are. You may -- if you test at the wrong time, you're not going to catch it.

DR. GOLDSTEIN: Dr. Mizrahi?

DR. MIZRAHI: One of the questions that I would have to the ophthalmology

colleagues is what is the clinical meaning of -- or translation -- the clinical translation of mild, moderate and severe visual field deficits? So does that mean that the mild patients would, for the most part, be asymptomatic with a non-clinically significant abnormality? The moderate ones, could some of them also be asymptomatic, or where along the way are we thinking that we could have a positive test in an asymptomatic or non-clinically significant patient?

DR. HECKERT: I think defining that's a good question. In fact, if you compare Dr. Sergott's definitions of mild, moderate, and severe, and Dr. Farkas -- Dr. Sergott has a much more rigorous -- I mean, the field's much further out as far as what he considered mild, moderate, and severe, so that I don't think there's necessarily agreement on that.

But I'd say that a lot of people probably where you do their visual field and you say, boy, they have a moderate field loss

yet in everyday life they're probably unaware of it.

DR. MIZRAHI: So in that circumstance, the answer to this question is yes, in the sense that we have a test that is positive in a circumstance at which it's clinically not significant.

DR. HECKERT: If you have an adult who can do reliable fields, yes, we do have a test that will pick that up at a time when it's meaningful in the course of their life.

DR. GOLDMAN: Dr. Lesar?

DR. LESAR: I had some comments, trying to answer those questions. There's a lot of components to it, so it's easiest for me to say can reasonable REMS be designed that can detect visual field loss early enough to mitigate the clinically important loss of function in a reasonable number of patients?

And you can use -- those are all ambiguous terms, but what I mean by "reasonable" is that, for instance, is this

test reliable enough? Is it accessible to enough patients? Is it cost effective? And that's one of the components that helps me. I'm trying to put my hand on all these issues. So can a REMS be designed?

We're talking about in the short term because we're talking about all the things that are potential. We're talking about whether we're going to approve this drug for the near term use, and then maybe issues that creates problems with the REMS. Perhaps we're asking too much for the REMS in this specific case. Perhaps we ought to look at the REMS rather as a risk prevention of -- what I call a risk re-evaluation tool.

That is, can we detect this at a reasonable time even if some patients do have severe damage, that we can then have them with their physician reassess the risk/benefit for the use of this drug? And of course underlying all this is, assuming that we started out with a patient who had a

reasonable risk/benefit ratio to begin with.

So I think it's easier to think of this test as a total can we design something that's reasonable to try to either mitigate the risk or at least allow appropriate risk re-evaluation.

DR. GOLDSTEIN: I guess that's sort of one of the undercurrents for a discussion that we'll have on the REMS a little bit later.

Let's see if we can just come to some general consensus about the issue of whether a clinically meaningful -- whether a visual deficit can commonly or usually or reliably be detected before it becomes clinically meaningful. In other words, if I was sitting across from a patient, could I tell him that if we do this, we'll be able to detect this visual defect before it becomes bad and then we can make a decision as to whether we need to treat you or not?

Or would I say to this patient that I'm not sure whether I'll be able to detect

this deficit before it becomes clinically meaningful and we may detect it when there's already a significant deficit for the first time?

So I'm trying to take the question to try to get to what the bottom line is. I don't know if we need to vote on it or formally vote on that, or just say whether you agree with that sentiment, because, again, we're here trying to give this guidance to the FDA.

Do we think, if you were sitting across from a patient with the information that you've seen, that you could tell the patient that, I think I can tell you that as long as we are measuring your visual fields, it's safe to do this?

Or could this occur despite us measuring your visual fields?

Dr. West?

DR. WEST: I think that going to Dr. Sergott's slide number CBC 10, page number 5

in 01-4 in the book, in the notebook that was given to us by the sponsor, that the important thing to remember is we're talking about a population with complex partial seizures that is not driving anyway.

I would agree with Dr. Sergott -- as an ophthalmologist, I would agree with Dr. Sergott's assessment of activities retained after onset of visual field defects.

The patients, at least in most states that I've practiced in, if you have a seizure disorder and you are not controlled, you do not qualify for a license. And so the only people that would lose the ability to drive would be people who had complex partial seizures who regained their license after a seizure-free interval and then lost visual field. That would be the only losers in this in terms of activities of daily living.

Most patients who have peripheral visual field defects do not present with the

visual field defect. They are found as a result of a screening examination, for instance glaucoma patients are typically not symptomatic, they don't come in saying, man -- you know, I think I've got glaucoma. I'm missing my peripheral vision. It's like a giant wake-up call for them because they've lost so much peripheral visual field that they have no idea that they've done it.

And so, I would feel comfortable sitting next to my neurology colleagues saying look-- you know, we think that as long as you can participate in a visual field test, we'll be able to pick it up when it gets to a mild to moderate level, and then a decision can be made about what to do at that point. But these are not patients who are going to lose their license because they've always been driving, these are patients who mostly, for the most part, don't drive.

DR. GOLDSTEIN: I guess part of this is what's the meaning of clinically meaningful,

what does "is" mean, but in general -- what we generally classify deficits are -- we talk about impairments where there's a neurologic finding or maybe an ophthalmologic finding. We talk about disabilities, effects on things that people do during their daily lives. And then we talk about handicaps where it effects them socially. So you're talking about either really handicapped level, that is it's impairing -- they can't get to work because they can't drive. This is, I think -- the thrust here first is, can we detect the impairment before it becomes clinically meaningful?

Dr. Katz?

DR. KATZ: All of this, I think, is predicated on our having some sort of a handle on how frequently you have to do this.

Presumably -- it seems as if there's a consensus emerging that we have a test, it can be relatively reliably done in most people, and it can pick up the lesion when done correctly, when it's relatively

early, whatever that means. But it's crucial to I think address the question of how frequently we can do it. This also, I think, speaks to Dr. Kramer's question with regard to the question of slow progress or rapid progress. If you did it every day, even if there was rapid decrement in visual fields, you'd pick it up, we presume. The question is, what's a reasonable frequency of performing this test so that we can, to the extent possible, ensure that we get it early.

DR. GOLDSTEIN: Do we have the data from what we've seen to be able to answer that question.

DR. KATZ: Whatever folks take into consideration when they give that answer, they'll do. So particularly, I guess I would ask the ophthalmologists, as experts in this area, to -- either based on their own experience or what we've seen and what we think we know about the natural history, so called, of the lesion. Frequency of monitoring, I think, is a

real critical issue here.

DR. GOLDSTEIN: Dr. Rizzo?

DR. RIZZO: So self report would be an important part of "clinically meaningful." And if you can't test somebody frequently, then you have to rely on self report. What tool was it that you used in order to obtain self report? Were these items from the VFQ25 or the VFQ, which is the standardized tool developed by the REM (?) Corporation in collaboration with the NEI?

And the other thing is, if you plot reported deficit against measured deficit, do they line up in people who are treated with the drug? In other words, are there a proportion of people who have a deficit and report that they have it and a proportion of people who report no problem but have a deficit who are then anosognosic, unaware of their own impairment, and the ones you would need to worry about?

DR. FAUGHT: The questionnaire that

was administered in Study 4020 was not a standardized questionnaire, it was a custom-designed questionnaire for that study that focused on questions related to vision -- to peripheral vision, so most of the visual field questionnaires -- most of the questions deal with impairments, with deficits that you would expect to occur with people because of a visual acuity impairment, so this was an instrument designed specifically for this study to look at peripheral vision.

As we said, the vast majority of subjects are unaware, subjectively unaware, of their deficit. It's not symptomatic. They don't come to doctors complaining of it. As I said, there was an eight-year delay in recognizing this problem partly because of that asymptomatic nature of the deficit.

DR. SERGOTT: I believe the issue that Dr. Rizzo raises about self assessment and those type of monitoring ones is a very good one. I take care of a lot of patients with a disease

called pseudotumor cerebri. Much like vigabatrin, fields can constrict. And it's unpredictable. Some could happen quickly, some slowly, but I actually teach my patients, their parents, whoever, how to do confrontation fields. It's a fairly easy thing to do.

I think we also have to return to the fact that -- you know, I think the data that we have while there may be a few outliers, does speak more for a slow progression. In my experience as a neuro-ophthalmologist now for over 25 years, when people lose vision suddenly, they're knocking on our doors, okay? I mean, we divide visual loss into three types -- sudden onset, sudden discovery of a preexisting deficit, which is possible, or slowly progressive.

My experience is, sudden visual loss, ischemic optic neuropathy, pituitary apoplexy, something that happens like that, they're right at you. There's no delay.

Russ?

DR. KATZ: That sounds like it's a central visual loss. What about significant precipitous visual field defect? Does that happen? And if it does, are people as aware of that as they are of central loss acutely?

DR. SERGOTT: And the answer to that is yes, based on my experience with the pseudotumor cerebri population. So these patients will be sort of smoldering along. You've known they have papilledema for a long time. All of a sudden, their field will come down, they get a little -- and they're in to see you right away. And then occasionally we'll see patients who have undiagnosed glaucoma, who as Dr. West said, all of a sudden they're aware of it. It was clearly going on before.

But I think with the monitoring program here and then the awareness of this, just like with glaucoma patients or glaucoma suspect patients, these patients will be the most carefully studied patients ever with any

potential visual field defect.

DR. GOLDSTEIN: Dr. Lesar? And if anybody just comes up to make a comment, please announce your name before you make it, if I hadn't recognized you specifically.

DR. NELSON: I think it was actually me that raised their hand perhaps, Nelson.

DR. GOLDSTEIN: Oh, okay.

DR. NELSON: We look alike.

DR. GOLDSTEIN: I didn't see it at all. I'm just following my commander here.

DR. NELSON: Actually, I just wanted to make a quick comment here. It's a little out of context now, but when we had talked about what the word "clinically meaningful" means and you, Dr. Goldstein had listed off a bunch of ideas, it reminded me that what I had been thinking about all along clinically meaningful means, is are we going to be able to catch it in time to stop its progression, and that's something that we have to answer, perhaps, in the next sub-question.

But all of the things we've talked about are important, but whether we can recognize it before it becomes clinically meaningful, meaning it will become meaningful later, is just, I think, as important.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: I think just to follow-up Dr. Nelson's question, along the same line, I think maybe it should be in the Risk Education Management -- but I notice the FDA mentioned, or at least I read from the document, there are some patients, they stop the medicine and still develop the VFD, so even if you capture while they are on drug, they may develop later, so whether someone can clarify that.

DR. GOLDSTEIN: Dr. van Belle?

DR. van BELLE: When I think about change and how to detect it, there are three ingredients that are necessary to be addressed. One is subject variability. Secondly, the change over time. And thirdly, the length of time that subjects are being observed. So if

you have a very slow change, you're not going to pick it up in a week, you may pick it up in three months. So I don't think I've seen the data that really would allow me to assess that within subject variability, the change over time and the interval of time. These would be the three things that I would need to see addressed specifically to be able to make a judgment whether or not it can be picked up.

DR. GOLDSTEIN: And to get to Dr. Katz's point, I guess we don't really have the data to tell us how frequently these evaluations would need to be done to be able to detect it early on or when it's relatively mild.

DR. KATZ: I'd be interested to know, just in general, what the Committee thinks about that, because I don't think I've heard lots of folks address that explicitly, but we're going to need to grapple with that question if we're going to contemplate approving the drug. We could impose some sort of draconian monitoring paradigm, but if we have little confidence that

it's going to get done or if it's going to completely preclude the use of the drug, it's not going to be useful. So I think we're going to have to deal with that question.

I just wonder what other folks on the Committee think -- if we have the information or if we don't have the information but every X months seems reasonable for some reason. I think it's a very important point for us to hear a discussion on.

DR. GOLDSTEIN: Let me just allow just a couple of responses to that, then I'd like to try to formulate this in a way and see if we can come to some consensus and then we'll take a break before I have an Excedrin headache.

Dr. West, did you -- want to ask Dr. Heckert about the frequency of monitoring?

DR. WEST: The frequency that would make sense to me would be something on the order of what the sponsor has suggested of every six

months. Every four months might also be reasonable as well. The other thing to remember is that this population would maybe have difficulty with transportation to visits since most of them don't drive, and so you may have missed appointments, and so four to six months would seem to be a reasonable interval.

DR. GOLDSTEIN: Dr. Heckert?

DR. HECKERT: I would agree with that.

DR. GOLDSTEIN: So to try to just summarize this -- and I don't think we actually need to vote on the question exactly the way it's written -- but from the sense that I'm getting -- and again, you can correct me if I'm wrong -- is that it appears that we think that if you were sitting across from a patient, you could tell them why monitoring -- by monitoring you frequently, every four to six months, we think that we can detect visual deficits before they become severe.

However, I can't guarantee that that's the case, that the possibility exists

that a severe deficit might occur that we haven't detected at an early phase. Is that a reasonable formulation, that we think in general, it could be, but we sure can't guarantee it because the data aren't there to prove that? Is that reasonable or not reasonable?

Dr. Weinstein, you're shaking your head no. I've got yes and nos.

DR. WEINSTEIN: That's a no. You know, I mean, wishful thinking doesn't make it so, and there's not even close the data to support that statement.

DR. GOLDSTEIN: Okay. Other opinions? So you would formulate it differently. What you would say is that we don't have the data to tell you that we can detect this at an early phase where it might be -- where -- at an early phase?

DR. WEINSTEIN: I view side effects as either being due to dose-related chronic exposure or idiosyncratic, and the two models that were up on the board there argue either or

and I don't know how you deal with the idiosyncratic, and I have no idea of what the percentage of them are idiosyncratic, and the bottom's going to fall out tomorrow.

DR. GOLDSTEIN: That's reasonable.

Other views?

DR. MIZRAHI: You know, I just don't know if that's a helpful point of view. I think that from my perspective, I think that it's reasonable to say this is what we're looking for, this is the best we can do in terms of the kinds of tests that we have, that it's possible that testing in this way we can make some detections that may have some meaning for you. But there are significant limitations because I do think there is some data to suggest that in part some testing can be helpful, but -- or predictive or at least can accurately suggest what is happening at the time.

But I think just to say we can't -- there is nothing to support doing any of the testing or making any clinically

meaningful statements about it, I think really is perhaps more of an extreme statement.

I would also say, just as long as the red light is on, that is that I still am not satisfied about the answer to the question why is our testing -- our first testing -- at six months, when the range of first onset of these problems is two to nine months?

DR. GOLDSTEIN: We're not talking about the testing schedule yet, but we'll get to that.

DR. MIZRAHI: I thought we were. I thought that was one of your questions.

DR. KATZ: Right, no, no, I think at the moment it seems to me that that is the primary question that we need to get a sense of the Committee's views on. How frequently -- and by the way, you could argue that the frequency could change over time. For example, the sponsor asserts that there's an increased risk

with increased exposure, so you could argue maybe less frequently in the beginning, more frequently as time goes on. I don't know, but we do need to get some specific recommendations. It could be sort of a range if -- you know, you could vote on whether or not you think every four to six months is the right thing, and then -- you know, we'll work out the details with the company afterwards but we need to get some guidelines.

DR. GOLDSTEIN: I'm trying to figure out what to formally vote on. Okay, well, again, let's see if we can sort through this a little bit.

We had two different sorts of formulations at least in terms of the general sense, one was that there's no data or there's -- we can't make a statement based on the data that's available. The second is sort of a -- may be a little softer saying there are some data, we think that you may be able to -- that we can -- that we may be able

to detect this, but we certainly can't guarantee it in any individual. Again, looking at the data, there were some folks that had relatively severe deficits that were picked up at the first screening.

Yes?

DR. DURE: Leon Dure, and I'm -- I'm confused. Are you saying that you sit in front of the patient and you can tell them that you can predict what they're going to do?

DR. GOLDSTEIN: No. That, you can detect.

DR. DURE: You can detect at that moment?

DR. GOLDSTEIN: Yeah.

DR. DURE: Is that how you understood it, Dr. Weinstein?

DR. WEINSTEIN: I was struck by the data that you just mentioned was at the first visit, they have the visual field loss, and I can't tell you if you had studied them a week before or two months before -- you know, you

would have seen it, but they're walking in the door asymptomatic with substantial visual field loss.

DR. GOLDSTEIN: Right, so to get to Dr. Katz's point -- you know, how often would you need to do the testing to be able to detect that? And I guess that's where the ophthalmologists said, well, every four to six months seems reasonable. Another opinion was that, well, maybe we need to do it closer together. Then when you do it closer together -- we don't have the data to be able answer those questions.

Yes?

DR. CRAWFORD: I've got a problem with this four to six months stuff. I mean, we're dealing with a population that's got intractable complex partial epilepsy that you've tried five or six drugs, and you're going to put them on vigabatrin and say I'll see you in six months? You know, that doesn't happen in the neurology circles. So we're going to see these patients

in two to three months.

DR. GOLDSTEIN: Not the ophthalmologist.

DR. CRAWFORD: Well, but you could do your confrontation and all that stuff.

DR. GOLDSTEIN: Dr. Katz, I think you got a sense. Okay? The sense is that the data are not sufficient to be able to give a very informed opinion. What it seems to be is that we're getting a bunch of different opinions from different perspectives that seem to be rounding around a period of time that seems reasonable based on what people's experiences have been.

DR. KATZ: I'm not sure that we're getting a consensus. Not that that's required either, but I'm not sure we've heard from the Committee. I think this may be one question where we can take a vote and maybe we can vote on a particular -- and remember, we're asking can you devise a monitoring regimen that you as clinicians think is good enough?

You know, we talk about (inaudible)

test, we're not at that point. We can't quantitative it. We have the data we have. And we're asking, in your judgment as a group, do you think every three to six months testing is good enough to take care of patients appropriately? That's the question.

So you can vote on a particular paradigm. You can vote on every four months. Is that adequate? But-- you know, I think we need some help and I think this is one where a vote --

DR. GOLDSTEIN: That's fine.

DR. KATZ: Where just polling everybody would be useful.

DR. GOLDSTEIN: Okay. Dr. Rizzo?

DR. RIZZO: Regarding frequency of testing, we heard an idea earlier today on monitoring that I thought was brilliant. I don't know if it works. It had to do with internet monitoring of visual fields. Does that work, and is it feasible? And if so, will it answer the question of you know, the problem of

how frequently we test?

DR. GOLDSTEIN: Dr. Rogawski? You were on our list here.

DR. ROGAWSKI: People have talked about this. It's not yet operational. It certainly could be, but I think part of the problem that we all face with patients in geographic terms could be done with simple video conferencing and telemedicine, and again, you'll be surprised how good you get with confrontation visual fields.

Getting back to this sort of duration or onset of the field, I think we have -- there's one patient in the literature in two months, the rest have been much further out, so I think that's where -- you know, this recommendation of six months, four to six months, came from. And again, we're going to have heightened awareness, I think as the gentleman said -- you know, the epileptologist is going to see these patients back in two months. And if there's any

question -- you know, we just go with that.

DR. RIZZO: So is in-home monitoring by Internet not feasible?

DR. ROGAWSKI: I wouldn't put any faith yet in an Internet visual field, but I would put faith in a video conference. You know, your child or the adult is having problem navigating. What's that from? Clumsiness or can't they see? That kind of actual history over the Internet is very good.

DR. GOLDSTEIN: Dr. Sleath, Dr. Kramer, Dr. Jensen, and then we're going to have to really close this part, at least for the time being, and take a break.

DR. SLEATH: I'm going -- just would like to say that if there isn't good enough data out there, I don't know how we can vote if we don't have the data, and I'll again bring up this Study 003, because to me, it's a red flag that Dr. Farkas talked about. It was stopped because Europe didn't require -- and I think you said it was in infantile seizures, and you

couldn't get enough patients -- one thought is should the FDA require a study similar to that? Because it looked like some problems were developing earlier than the company has kind of said in the background material. So that's just a thought I had is, do we really need to have a discussion about what data is needed so that we could vote on an adequate time period?

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: I'd just like Dr. Farkas to clarify your interpretation of -- I thought I heard you say that the data we have is primarily cross-sectional and not longitudinal. And that would suggest to me that we don't have the data to address this issue about whether we could prevent it. Could you just clarify your interpretation of the totality of the data?

DR. FARKAS: Yes. Well, I think I should state first that my interpretation of the data is my interpretation of -- and I think that we're asking -- if your interpretation or the Committee's interpretation of the data was

similar to the FDAs.

But I can say, again, what my or FDA's interpretation of the data was, and that is that particularly from Study R003, which was the prospective study that we felt was the best designed out of the studies, even thought it was small, there were patients that were diagnosed at the first diagnosis with moderate severity of visual field deficits after every three month monitoring.

We were not aware of any way to -- from the data that we have, figure out how they could be diagnosed earlier although Dr. Katz has mentioned that at some point of very frequent monitoring in patients how are doing field test well, presumably or possibly that could be improved upon.

DR. GOLDSTEIN: Dr. Jensen?

DR. JENSEN: I'm going to make a stab at just -- I realize that -- my first question was I don't think that the sponsor, per se,

showed data to answer this question. That's why it's on the table. But having heard this discussion from experts, it would seem to me that you could make some educated decisions based on all of the other information coming from the field of ophthalmology and these studies that are complete and partially complete, and that one could say, well, obviously you'd want a baseline. Then we heard that two months was the earliest that had been shown.

It might be that there might be onsets earlier than two months, but then you'd want something at two months or prior to two months, maybe six to eight weeks, for a first screening. And then we also would need to build in this concept of there is some sort of peak incidence effect around a year. Knowing that that's a hot spot, you'd have to take that into account in terms of your frequency.

And we also heard that it

progresses, perhaps less -- there's less incidence out after that one year point, but that it can go on up to many, many years. So you would have to build in some sort of a more relaxed, potentially, schedule of screening.

We also heard that there is questionable evidence, certainly evidence that has yet to be refuted, that there might be a progression after discontinuation of the drug therefore we have to build in some sort of a screening of patients once they had been discontinued. So I would just put that out.

I think that -- you know, we could go on arguing forever, but there is potentially something you could map out, a structure that, I think, using the Goldman technique would be -- or the visual field perimetry testing that has been discussed here at length, a not unreasonable approach given not what the sponsor has shown, but this discussion. I'm just putting it out

there as my opinion.

DR. GOLDSTEIN: As you said, we could continue this discussion for quite a long time. What I'd like to do is maybe -- I think we probably should have a vote on letter B, but maybe just change it just slightly and say, are there data to show that the visual defect can be detected before it becomes clinically meaningful? That way, we're taking the sponsor's data out of it and we can take all of the other discussion, the discussion that we had.

We can vote yes, that that is true, no, that we don't believe that's true, or abstain, which to my understanding, from what I'm told, that means that you don't think you have enough data to be able to answer the Question 1 way or the other.

So if the Committee agrees, why don't we state it that way? Are there data that the visual loss can be detected before it becomes clinically meaningful? Okay? And

press your buttons. And you tell us when we're done. Do we hold them? Two more people. Hold them down. Okay. Yes, 14; no, 7; 3 abstain. Well, there you go.

When you've got good data, you can really come to a conclusion. So now we have to go around.

Let's see, let's start on this side this time since we went the other way the last time. We have to do the roll call.

Dr. Nelson?

DR. NELSON: I reluctantly voted yes. Do you want an explanation or should I just leave it at that? That's probably fine? I think we've heard enough from me.

DR. GOLDSTEIN: Who's next on this side?

DR. LESAR: Lesar. No.

DR. GOLDSTEIN: Dr. Kramer -- oh, Dr. Gardner, I'm sorry.

DR. GARDNER: Gardner. Yes, based on the discussion.

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: Kramer, no.

DR. CRAWFORD: Crawford, abstain, but not for the reason the Chair stated. I abstained because I believe the answer is yes in some cases, no in others.

DR. GOLDSTEIN: Dr. van Belle?

DR. van BELLE: Van Belle, no.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: I abstained.

DR. GOLDSTEIN: Dr. Balish?

DR. BALISH: Balish, no.

DR. GOLDSTEIN: Dr. Rizzo?

DR. RIZZO: No, one time.

DR. GOLDSTEIN: Dr. Jung?

DR. JUNG: Jung, yes.

DR. GOLDSTEIN: And I voted yes. And next is Dr. Sleath.

DR. SLEATH: Sleath, abstain.

DR. GOLDSTEIN: Dr. Vega?

DR. VEGA: I voted yes.

DR. GOLDSTEIN: Dr. Rogawski?

DR. ROGAWSKI: Rogawski voted yes, although I am very sympathetic to Dr. Weinstein's position. I was convinced by the discussion in the sense that I think that this is an evolving process, and as we go forward, we're going to be getting more information and we'll be able to sort of tailor the way that we approach this problem. And so I would hate to see that on this specific issue we sort of torpedo the whole ship.

DR. GOLDSTEIN: Dr. West?

DR. WEST: West, yes.

DR. GOLDSTEIN: Dr. Heckert?

DR. HECKERT: Heckert, yes.

DR. GOLDSTEIN: Dr. Gorman?

DR. GORMAN: Gorman, yes.

DR. GOLDSTEIN: Dr. Snodgrass?

DR. SNODGRASS: No, but it doesn't mean the drug couldn't get on the market.

DR. GOLDSTEIN: Got it. Dr. Dure?

DR. DURE: Dure, yes.

DR. GOLDSTEIN: Dr. Chugani?

DR. CHUGANI: Chugani, yes.

DR. GOLDSTEIN: Dr. Jensen?

DR. JENSEN: Yes.

DR. GOLDSTEIN: Dr. Weinstein?

DR. WEINSTEIN: I voted no, but with the idea that the data someday will be available.

DR. GOLDSTEIN: Dr. Mizrahi?

DR. MIZRAHI: Yes.

DR. GOLDSTEIN: Dr. Hirtz?

DR. HIRTZ: Yes.

DR. GOLDSTEIN: Mr. Bartenhagen? Oh, sorry, you're not voting. Sorry. Excuse me. Okay, so you've got our sense on that.

Now, the other thing that I'd like to do just before the break is Dr. Katz also asked us to take a vote on what a reasonable testing regimen might be, because we've had quite a variety of things. Let me propose one as a straw person first, and then if everybody's cool with it, fine. If not, it's open for discussion.

So one we heard was -- excuse me? Oh, sorry, she needs to summarize the vote for the record.

SPEAKER: That was 14 yes, 7 nos, 3 abstentions, for a total of 24.

DR. GOLDSTEIN: Very good. So one was a baseline, before treatment, then something at two months, and then every four to six months thereafter with -- there was some discussion as maybe it needs to be closer together at a year. But let's -- for the purposes of discussion, let's say two months then every four to six months thereafter.

Does that sound reasonable or not?

Dr. Gorman?

DR. GORMAN: Could I suggest the first one at three months, because at that time, there will be a substantial number of patients off of therapy.

DR. GOLDSTEIN: That's fine. Three months, then every four to six months thereafter. Good.

DR. RIZZO: I'm sorry. Have you been taking anything? As important as how frequent or what test to give, I'm not clear on that, so it makes it hard for me to be able to vote.

DR. GOLDSTEIN: Well, let's assume that it's Goldman perimetry, because I think that's what we heard was probably the most commonly done. Is that reasonable? Yup.

DR. CHAMBERS: Mr. Chairman, I don't think Goldman is anywhere near as common as Humphrey, which is a threshold field, and Goldman's going to require -- I mean, if you want to recommend it, by all means, recommend it. But just bear in mind, Goldman is technician dependent and nowhere near as common.

DR. GOLDSTEIN: Let's leave the specific modality maybe for further thought, but just in terms of the frequency. So what we have on the table, I guess now is baseline three months then every four to six months thereafter.

Yes, Dr. Mizrahi?

DR. MIZRAHI: Just to emphasize Fran's

point that thereafter should include a period after therapy.

DR. GOLDSTEIN: Yes.

DR. MIZRAHI: And as yet undefined.

DR. GOLDSTEIN: Okay.

DR. GORMAN: Could I just say one thing about baseline? And maybe this is something you would implore to insurance companies or what not, but your baseline may have been more than one field because of the learning phenomenon. It really takes, probably three fields before you really know how to do it so I think it may be repeated in real short order when you first start.

DR. GOLDSTEIN: Again, a technique of what an ophthalmologist would consider an adequate baseline, again, we'll leave to the experts. Okay, so let's try that. And let's just do it maybe by a show of hands first. If that seems reasonable given all of the problems we have with the data, yes?

I'm sorry.

Dr. Kramer?

DR. KRAMER: I'm sorry, but I need to ask a clarifying question. What I'm struck with is we're coming up with sort of the perfect regimen to try to detect this early before it becomes clinically meaningful, but in the big picture, I want to know if we're making -- taking a vote that will indicate something tied to this REMS program that could defeat the accessibility of this drug to patients who need it, and having been someone who's evaluated the effects of risk management programs like Tikosen (?) we can design the perfect program and we will assure that it's safe because nobody will be able to continue on the drug because they can't adhere to what we recommend.

So I want to make sure that we're doing a theoretical discussion about what you think might be the best from an ophthalmologic point of view and not tying our recommendation to a requirement.

DR. GOLDSTEIN: The REMS program is after the break.

DR. KRAMER: Okay.

DR. GOLDSTEIN: This is from a theoretic standpoint what we think the most reasonable monitoring would be given the science. Okay? So, baseline, however done, three months, then every four to six months thereafter, including some period after the drug was stopped. Reasonable? Yes, no? Yes? Any nos?

Okay. Good deal. Abstain? Again, this was a show of hands. We're not doing a count here. So I think you saw that most people had their hands up thought this was reasonable. There were a few folks who didn't raise their hands and that was abstaining. Nobody said no.

Okay, look, let's take our 15-minute break. I'm sorry it was late, but I think we got over a major hump here, and hopefully we can get the rest done.

Quarter after.

(Recess)

DR. GOLDSTEIN: Very well. Let's get restarted for hopefully -- to try to deal with some of the outstanding issues. When we left off, we'd gone through -- at least through Item B on Question 1. There are still Items C and D. What I'd first like to do is see if we can deal with these sort of succinctly. I think the data are what the data are, so I don't think there'll be a lot of discussion about it. But let's take a look at C first.

Has the sponsor adequately shown that dis-continuation of treatment halts the progression of visual loss? To set that up, I guess there were at least some cases where there appeared to be visual loss that may have progressed after the drug was stopped, and that was part of the reasoning behind saying that the monitoring should continue after the drug was stopped.

So, any comments about that? And

again, if I'm not presenting it correctly, please correct me. Okay, great. So having said that, let's see if we have consensus. And if not, then we can do a vote.

So, has the sponsor adequately shown that dis-continuation of treatment halts the progression of visual loss? Yes? No? Okay.

So for the record, the consensus was that no, the sponsor hasn't adequately shown that dis-continuation halts progression.

Question D was the sponsor asserts that the drug does not cause central visual loss. Does the Committee think that the sponsor has adequately shown this? And again, just to quasi-summarize this, some of the testing that was done seemed to me to be done for peripheral visual loss, in that there were at least some issues that were raised in the FDA presentation about the possibility of central visual loss, although

that clearly was not one of the things that's come out a lot in any of the other studies that have been done.

So discussion about that -- about the point? Yes.

Dr. Mizrahi.

DR. MIZRAHI: Could Dr. Farkas remind us of some of the data to this point that you reviewed this morning? You did show some data about central visual and acuity loss.

Is that true?

DR. FARKAS: Yes, that's true.

DR. MIZRAHI: And if I remember right, there were some cases of --

DR. FARKAS: Slide 14 from my presentation. So that was a case series by Miller et al. Anyway, the concern on our part was that although the case series can't tell us how frequently an effect or an adverse effect on acuity might occur, in the 32 patients on vigabatrin, 12 had apparently reduced visual acuity, and that was versus presumably

well-matched controls as well as possible in such a study design which showed normal acuity.

I guess Slide 15, too, I should say. Although it's really impossible to know -- even for, I think, an experienced ophthalmologist to know -- what visual acuity would correspond to a certain appearance of the retina. I think that's generally safe to say. Supporting that is that the macula is abnormal in some patients who are on vigabatrin.

DR. GOLDSTEIN: Dr. West.

DR. WEST: I think that -- I think that although there was subnormal visual acuity that was measured, it was not an accurate visual acuity. And I would not make the leap of faith to say that therefore, it causes low visual acuity. I trained with Neal Miller, and he does not refract. And those visual acuities, if they are not best corrected visual acuity, you don't have crap for data.

DR. FARKAS: Well, I think another

point that I would --

SPEAKER: Thank you for the medical terminology.

DR. WEST: And I think that there's contradictory data for the Glasgow study that shows that the visual acuity is normal in patients who are taking vigabatrin. And that was patients who were actually refracted.

DR. FARKAS: We don't have enough information about the Glasgow study to know if it was capable of detecting mild or possibly even moderate visual loss. And I think we recognize that there aren't patients who have 2100 or 2200, and that's kind of very rare. But I think overwhelmingly, the studies that have been conducted have not been designed to detect mild or moderate visual loss. That's what our findings are.

DR. GOLDSTEIN: Other comments? Okay, so the question then is, the sponsor asserts that vigabatrin does not cause central visual loss. Does the Committee think that the sponsor

has adequately shown this? That's the question.

Let's again try for a consensus first, and if not, then a vote. So the first is yes. Does the Committee think the sponsor has adequately shown that vigabatrin does not cause central visual loss?

Yes? One. No? Okay. So the consensus looks like no, but there seems to be a fair number of people who have no opinion. I'm happy -- if the FDA is satisfied with that, that's fine. If you'd like us to take a formal vote, we can do that. Dr. Katz is shaking no. Okay, so they're satisfied with the sense that they got from the opinion.

Okay. So let's switch now to Question 6, which follows from this. Are there additional data related to the visual loss that should be obtained prior to approval if the drug is approved? So prior to approval. Now, remember, as part of the risk mitigation and evaluation scheme, one of

the things is that every patient will be in a registry, and that will involve the visual field testing that we spoke about. So the question here is should additional studies be done before that point? That, I think we do need a little bit of discussion about. Comments?

Maybe not. Okay, I have no -- I'm sorry, Dr. Weinstein, did you --

DR. WEINSTEIN: I was going to say --

DR. GOLDSTEIN: And if you don't have any points, please make sure -- Dr. Mizrahi, can you just turn your light off there so I don't get more confused than I already am.

DR. WEINSTEIN: I don't think anybody wants to kill the drug. And the problem is that once we start adding on things to be done, in essence, we're killing the drug. And that's why I don't think you're seeing much discussion.

DR. GOLDSTEIN: Okay. So let's get a consensus on this one then. Are there additional data related to visual field loss

that should be obtained prior to approval if the drug is approved?

Yes? No? Okay. Thank you. You have your consensus there. The consensus, I think, in general was that no, additional studies don't need to be done before approval, if that's the way that we go.

Okay. So --

DR. ROGAWSKI: But, you know, I think the caveat should be that studies should be done if the drug is approved.

DR. GOLDSTEIN: That's right.

DR. ROGAWSKI: In the post-marketing.

DR. GOLDSTEIN: And that was the proviso that I mentioned before saying that, that as part of the risk scheme that we'll be talking about next, one of the key points was careful monitoring of vision at the frequency to be determined. But we already said what we thought might be reasonable for that.

Okay. So let's turn then to Question 4, I think. So we had already said

earlier that there were circumstances under which we thought that the drug could be approved for at least some populations. And we talked about the risk evaluation and mitigation strategy that was presented. So we have -- can you put up five, please? Sorry, four. I'm sorry.

So we have a couple of subquestions now. Should it be made available only under restricted conditions -- that is to certain practitioners, restricted distribution and educational programs, special training? And I believe that there are elements of that that were all included in that scheme. And then should continued access be linked to ophthalmologic monitoring.

Dr. Katz.

DR. KATZ: Yeah. Again, I'd recommend at this point -- because we have a pretty good idea, I think, of what sort of monitoring people think is reasonable and that sort of thing -- I think at this point, I would suggest that we go

back to the effectiveness questions.

DR. GOLDSTEIN: Okay.

DR. KATZ: Because that's the other half of this. And I guess Question 3 -- we're interested again in the question of do you think that the sponsor needs to obtain more data on the question of effectiveness in refractory patients. Should there be comparative data -- direct head-to-head comparisons either to something the patients have failed already, as Dr. Temple was talking about earlier, or to some other agent?

Or do we have enough efficacy data at the moment in hand to be able to write adequate labeling in terms of who should get this drug? I think those are the next critical questions, maybe even the last set of critical questions.

DR. GOLDSTEIN: So -- and you're framing that in terms of before approval, an additional controlled study in some population before approval. Okay. It's open for

discussion.

One of the groups again that was discussed is -- you know, that we were talking about earlier, are patients that are refractory to other drugs. And we talked a little bit about the problems with defining that. Would the type of study that, for example, Dr. Temple had mentioned earlier -- would that be a reasonable thing or not a reasonable thing to do before a drug like this was approved?

Dr. Jensen.

DR. JENSEN: Well, I guess one of the issues in answering that question is it would depend upon the conditions. It's interwoven with what would be the conditions that you would approve the drug for. If you said we would only approve the drug as like a fourth-line agent after -- you know, X number of other drugs have been put in front of it arbitrarily because of the cost and the extent of -- you know, the extent of the monitoring that's going to be

necessary, that would, for instance for me, change what I'd want to see in terms of studies. I might feel I didn't need to see any studies done.

However, if we said, yes, it could be just used as management after somebody has failed only one drug, I'd kind of want to know a little bit more about how it stacks up against the 10 new drugs.

So I think that -- you know, it's interwoven a bit. Maybe we need to think about both questions at the same time.

DR. KATZ: Again, we're interested -- and these are intimately and extricably related.

I completely agree. So we are interested to know what you think -- if you think you have enough data in hand from the effectiveness point of view to approve it, what sort of indication do you think it should get? Should it be last resort kind of a thing or try four other drugs first. So it

would be useful to hear what people think about that.

DR. GOLDSTEIN: Okay. Dr. Kramer.

DR. KRAMER: I guess I'd like some input from the epileptologists on the Committee. But one of the things that strikes me is that when we do these studies, we're looking at populations and average effects. And I was struck by several of the comments that suggested that these patients respond in very individual ways, and there can be a new drug that suddenly has an effect when nothing prior to it has worked. But that may not be the same for someone who looks identical but doesn't respond in that way.

So with the number of available agents that come before something for intractable epilepsy, the permeatations and combinations of what you could try are numerous. And the fundamental question for me is how restrictive do we plan to be in terms of having a very detailed requirement

for everything that has to happen before someone can use this drug, versus recognizing it has effectiveness in some individual patients. There has to be clear risk communications to doctors and patients, and leave it up to the doctors and patients. So I'd like a sense from those of you who treat these patients where on the spectrum you feel that you are.

DR. GOLDSTEIN: Dr. Dure.

DR. DURE: Yes. And I -- this follows up with Dr. Kramer's point, because it goes back to what Dr. Mizrahi said a while back, and that was he knows it's refractory -- he just sort of knows. It's like what Potter Stewart said about pornography: I know it when I see it.

And I don't mind sitting here and listening to their discussion about this, but I know that in my own practice that I will refer to my epileptologist to make this decision. And Dr. Faught said -- one of the first things that he said was this is going

to be a fairly restricted population of patients who will be cared for in tertiary centers or quaternary centers. And I know that there are issues related to access, but the simple matter is that these patients aren't typically cared for -- they may have to go a long way to be cared for, but that's what they have to do.

So again, I don't know if hearing -- I don't know if we'll get consensus from our epileptologist about when they would use vigabatrin, but I would trust their judgment.

DR. ROGAWSKI: I found this concept of -- it was -- I think the idea was for special use. There was a term that the previous sponsor, when they submitted their package to the agency, used as a term to define how this drug would be used. And as part of that, they indicated that the drug wouldn't be marketed in any way. It would be made available, but that the drug wouldn't be promoted and marketed. And

given the difficulty that I have in defining which patient populations this agent would be useful for and which it's appropriate for, I think that we could get around the problem of having it be prescribed for in appropriate patients by making that requirement that the drug not be promoted or marketed.

And that gets around this problem of having to define specific --

DR. TEMPLE: Forget it. We don't have that authority yet. Maybe we'll get it.

(Laughter)

DR. ROGAWSKI: Could the sponsor voluntarily --

DR. TEMPLE: Yes.

DR. ROGAWSKI: Propose to the Agency, the way that they did -- the previous sponsor apparently did do that.

DR. TEMPLE: The sponsor can do that voluntarily, but we can't make that a condition of approval.

DR. ROGAWSKI: Right.

DR. TEMPLE: We might want to, but we can't.

DR. ROGAWSKI: But to me, that seems like it would solve this issue of having to define precisely, because then it would only be used by physicians who were appropriately educated in presumably how to use the drug.

DR. TEMPLE: Can I ask a question? I mean, I know this is hard, but some people from the audience before have suggested that you really should try everything else first, or almost everything else, or whatever "everything else" means.

Is that where people are thinking? That's easy enough to say in labeling.

You can't force it. But you can say you should have tried five or six other drugs before you undertake this. Is that what you're thinking?

No. Well, what are you thinking? And also, what aren't you thinking?

DR. GOLDSTEIN: Dr. Hirtz.

DR. HIRTZ: Well, I agree with most of my child neurology colleagues, in the sense that I think that the use of this drug would be very analogous to what people are thinking about when people are thinking about using surgery for intractable epilepsy. And the decision is generally made that it's intractable after several drugs, but there are various definitions of intractability, and we can argue about that.

But there's a tremendous risk to surgery, and also a potential benefit. And there's not enough data, but there is some data on surgery. And I think that's where we are now. We'd love to have a lot more data for sure, but we know that it does work for some people. And to deny it to those people for another two, three, four years while we get the data I think would be wrong. And I think we can look at it as we would when we consider surgery and use those kinds of cautions.

DR. KATZ: One option new had

discussed earlier -- years ago actually I guess with the other sponsor -- was to indicate it as, in a sense, a last resort prior to surgery. In patients in whom epilepsy surgery is being considered, try this instead. Or -- you know, before.

I'm not advocating that we do that, but that's a way to essentially state that this is sort of a last-resort drug, but it doesn't say you have to have tried seven drugs prior to this. It's sort of an operational definition. It's going to vary from practitioner to practitioner, but it's in that sense sort of a movable bright line, if you will. Again, it's just another way to sort of get at this.

You might want to think about that.

DR. GOLDSTEIN: Dr. Mizrahi.

DR. MIZRAHI: Just a comment about this concept of I can't define intractability but I know it when I see it. And it's not that any of -- well, myself -- that great a

clinician. It's just that that's the real limitation of the practice of epileptology now.

So -- but what I think is actually an operational -- well, something that helps us in a different way is, rather than focus in on defining intractability, is to say that this is a drug for patients who are intractable, and that the break or the governing issue for its use is really going to be a well-defined risk, because I think clinicians are really going to think twice about using this drug when the risk is really very clearly stated, that 40 to 60 percent of the patients could wind up with irreversible visual field deficits. And who wants to go there if you have something else that could work equally as well?

I think as far as saying, well, you need to try this many drugs before you use this drug, or this is the drug of last resort, well, there may be times where you see where you're headed, and that it's

perhaps a patient who is intractable but is not an epilepsy surgery candidate because they're multifocal or generalized, and that's where you're going. And so rather than spend a year of trial and error and what we heard of lost time, we go directly to the end of the line and see if we can do something better.

So you know, I hate to sort of put it in sort of the -- this sort of indefinite category, but I think really the best that we could do is say medical intractability, define the risk, and then let the physician and the patient understand and make the risk versus benefit assessment.

DR. TEMPLE: But you don't have any data that this is going to work any better than drug number seven. They haven't done that.

DR. KATZ: That's right.

DR. TEMPLE: They haven't done that trial.

DR. KATZ: And you've defined the

field of epileptology. That's what we do.

DR. TEMPLE: Let me apologize. But why does it horrify you so much to say something like ordinarily patients should have been tried on a number of drugs from a number of drug classes before you resort to this one?

DR. KATZ: Well, I think that's a reasonable thing to do.

DR. TEMPLE: Okay.

DR. KATZ: Rather than saying to be -- to give a specific number or a specific glass of drug.

DR. TEMPLE: Okay.

DR. KATZ: But -- yes, I think that that's a reasonable way to look at it.

DR. GOLDSTEIN: Dr. Gorman.

DR. GORMAN: Yeah, I'd like to follow up on that comment, because it reflects what I was thinking as well. There's another risk we haven't talked about much, which is the risk to the physician prescribing this drug, which I think we'd all be aware of. That I don't think

this is going to be the first-line therapy for any clinician unless there becomes a condition, besides the one we may be talking about tomorrow, where this clearly seems to be an extremely effective therapy. If I remember the slides from this morning, it looked like 12 percent of people who have been on other therapies became seizure-free on this medicine. Not a universally overwhelming response, but for that 12 percent, really important.

And I feel very comfortable with my seizure doctors surrounding me because I can't say those big words, being a simple country pediatrician.

To find a definition between more than two and less than last, because as data evolves, that this may in fact become the drug of choice for another subset of seizures that occur in adults, I would hate to have their hands tied.

DR. GOLDSTEIN: Dr. Chugani.

DR. CHUGANI: Yes, I just wanted to

echo what Dr. Mizrahi said. I think the last drug before surgery is very restrictive. I certainly -- I can tell you from my own practice, I would certainly use vigabatrin for complex partial seizures before I went to vagal nerve stimulation, for instance. I certainly would do that first.

And then there are special populations. I know we're talking about adults, so there are adult patients over the age of 18 with tuberous sclerosis where this might come relatively early as one of the -- maybe the third or fourth medication rather than the sixth or seventh. So I think we've got to take that into consideration.

Now, tomorrow, we will hear that in certain pediatric populations, it's the treatment of choice. But that's a different situation. We're talking about adults now but -- you know, there are a lot of TS patients.

DR. GOLDSTEIN: Dr. Weinstein.

DR. WEINSTEIN: Quickly looking at my database of patients I've seen over the last decade, I've had 47 kids that have been on vigabatrin. And it's always sort of down towards the bottom of the list because of the difficulty in getting the drug.

But at the same time, looking at what happened to those patients, lord knows they failed more than three, more than four, and by adding more and more numbers of drugs that you have to fail, you end up with a population that nothing is going to fix. And I think that's true of the population that I chose to treat with the drug.

But I agree. Somewhere between two and number 15 is the right number. And you're never going to solve that. And all you can do is just -- and again, if you emphasize the ocular abnormalities, people make that decision.

DR. GOLDSTEIN: Dr. Rogawski.

DR. ROGAWSKI: I just wanted to

re-emphasize the point that Dr. Temple is making, that in my opinion, we really don't understand the population of patients that is going to benefit from this drug. And I think it's also important to point out that we don't want to give the impression in the labeling or in the promotion of what have you that because this drug is so special and needs to be handled in such a special way, that it necessarily has greater efficacy to go along with that toxicity.

I don't think there's any evidence for that. In fact, I think the evidence that's available with head-to-head comparisons suggests that the drug is perhaps somewhat less effective in populations of patients. Not to say that there aren't individuals who respond to it very well. So I think that needs to be considered as we define how this drug is going to be developed.

And also, just to comment on this issue about last resort before surgery. I

think you've heard from other Committee members that this probably isn't such a good idea, because there are many patients who are intractable who aren't surgical candidates.

DR. GOLDSTEIN: So let me try to phrase 3A in a way that we can see whether we have consensus on it, or a vote. And if we were saying the appropriate population, given again what we know that it would be patients with epilepsy that are refractory to multiple other anti-convulsants, and leave it at that.

And part of this will be sorted out because of the toxicity issues and the monitoring issues.

Does that sound reasonable to people? Sorry? Somebody had their hand up. No?

Dr. Gardner. I'm sorry.

DR. GARDNER: My objection to that is something the FDA is not supposed to consider but we can, and that is that if we phrase something having to do with multiple other or

five or something number, then from the standpoint of reimbursement companies will decide that there needs to be demonstrated failure on some number of drugs. And so I just want to heighten our sensitivity to that in terms of accessibility and reimbursement issues.

Can we accomplish what we were trying to do here without specifying something that is going to make patients jump through hoops over a period of time for their insurance companies?

DR. GOLDSTEIN: Unfortunately, I guess given the data that we have, we sure can't come up with a number. And as said, for the reasons we discussed, we can't say that they need to be just ready for surgery, and this is the last option.

DR. GARDNER: But you did say multiple, and that can be defined. Is there a reason not just to say as the epileptologists have said, intractable or --

DR. GOLDSTEIN: The problem is that we

can't say that all these patients are going to be cared for necessarily by epileptologists. They may be by neurologists -- you know, general neurologists. I'm trying to -- again, I'm trying to walk a line here between what's reasonable -- trying to come up with a line that's reasonable.

So the way I had phrased it was refractory to multiple anti-convulsants without defining what that number is. And unfortunately, this is stuff that we deal with on a daily basis dealing with insurance companies. Getting a MRI, getting a CT. All of this stuff has to be approved. It's always a battle.

So I think it's going to be the physician dealing with the insurance company, and there's just no way around that. We're not going to come up with a number here.

Yes. Dr. Chugani.

DR. CHUGANI: Can we downscale multiple to several?

DR. GOLDSTEIN: Sure. That's fine. I don't have a problem. I guess they're getting the sense of what we're trying to get at and that's the real issue. The wordsmithing, the FDA will deal with. Again, it's the sense of what we're trying to say here.

Dr. Dure.

DR. DURE: Yes. I guess one thing I'd like to add would be multiple or several -- I don't know the right adjective, but they need to be good trials. There is a variation -- well, that's the problem. You shake your head, but our Question No. 4 talks about restricting availability to practitioner-type. And again, although I know that's an issue with respect to access, that may actually be a desirable goal.

But that is one way to approach this problem -- is to limit this to -- you know, epileptologists.

DR. GOLDSTEIN: Okay, I guess we can deal with that in the second part.

Okay. So let's just change

refractory to several. Sorry, the multiple to several. So a patient population that's refractory to several other anti-convulsant drugs. Okay. I don't see anything, even in my hemianopic fields. Okay, very good.

So would you like a vote on that or can we just do by consensus? Just consensus will work. Okay, is the consensus that that's a reasonable population to approach here? Yes? No?

Okay, so for the record, the consensus was yes, that's a reasonable population that would be appropriate for this drug.

The second part of this -- should additional effectiveness comparative data be obtained specifically in this population of patients that are refractory to several drugs before approval? Is that right?

DR. KATZ: Again, I think -- we've been talking about -- there's a couple of issues here that we're sort of subsuming under the sort

of refractory. There's good documentation that patients haven't done well on multiple drugs. And then just do a regular add-on study. That's one sort of way to look at refractory.

The other is to then re-randomize patients to something they failed on, which is a completely different type of evidence. This question is sort of more or less asking about the latter, but we're really interested in knowing whether or not there's any other kind of data -- any other kind of controlled trial that the sponsor needs to do before we can approve it. So I would just sort of broaden that to include anything else.

DR. GOLDSTEIN: Okay. Comments? Okay. Let's -- I'm sorry, Dr. Sleath. Slealth. I'll get your name right yet. Sleath.

DR. SLEATH: You can call me Stealth, Sleath, whatever.

Just from the risk communication side in terms of studies I'd like to see is I would like to see -- the company -- the

sponsor talked about readability, but I'd like to see studies on patient comprehension of these materials that are developed for them and for the physicians.

And also I'd like to just suggest that maybe the Risk Communication Committee review the materials that are developed, because I was struck by in here -- I've heard numerous times today leave it to the physician and the patient to talk about risk-benefit, but unfortunately, that doesn't always happen. As in our materials, one patient died because the parents misunderstood the labeling.

So I think although the people in this room probably are great communicators, not all physicians are. So I think it's very important that these materials be tested for comprehension, and as Dr. Vega already said earlier, that maybe even sixth to eighth grade is too high of a level. And that's kind of a broad range in itself. Maybe it

needs to be sixth grade or lower.

DR. GOLDSTEIN: Okay. Would you want that done before the drug was approved, or could that be part of the development of the risk?

DR. SLEATH: I think it needs to be done before it's approved if you're going to have this registry and people consenting. I don't think something like that takes that long to do.

DR. GOLDSTEIN: Okay. So let's put that on the side for a sec. The question was, should a comparative effectiveness study be done in this population of patients that are refractory to several other anti-convulsants in one or another design mechanisms?

SPEAKER: Before.

DR. GOLDSTEIN: Before approval. Yes. Okay. Let's try this one. Yes? No? Okay. I think again, for the record, the consensus of the Committee was that no, an additional comparative study in the group of patients that are refractory to several other anti-convulsants

doesn't need to be done before approval.

Okay. Okay. Actually, before we go on to four and five, there's one other toxicity that I think we need to deal with that we sort of talked about before but we didn't really finish with. And that was the problem with the intramyelinic edema that was seen in animals.

The first question that they had -- this is Question 7 -- is does the Committee believe that this has any clinical consequences in adults? And my sense from what we've heard was that we just don't have a clue, because this hasn't really been studied in any way.

It was a radiographic finding without necessarily any clinical correlation to it. And also, at least on the MRI study, again, given the techniques that were used that there was no difference between the patients that were treated and the patients that weren't treated.

Is that a correct summary?

DR. KATZ: I missed -- I apologize -- at the beginning what you said, but I thought I heard you say something about it was only a radiographic finding. But I didn't hear what the preceding phrase was. This was a finding seen histologically in animals. In three animal species. That wasn't radiographic.

DR. GOLDSTEIN: No, no, no. In humans. It was a radiographic finding that I believe --

DR. KATZ: In humans, in adults --

DR. GOLDSTEIN: Right.

DR. KATZ: In adults -- we don't seem to think that there is a particular finding on MRI.

DR. GOLDSTEIN: Okay.

DR. KATZ: We agree with the company on that point.

DR. GOLDSTEIN: Very good. So does the Committee believe that the findings seen in animals have any clinical consequences in

adults? And I guess the answer -- the question is yes, no, or there are no data to say whether this is of any clinical significance or not.

So let's try this one. I think we can dispense of this one quickly also. Yes?

DR. ROGAWSKI: I think the question needs to be wordsmithed just a little bit.

DR. GOLDSTEIN: Okay.

DR. ROGAWSKI: We don't know whether it has any clinical consequences in adults. But there's no evidence to suggest that it has any clinical evidence in adults.

DR. GOLDSTEIN: That's right. Yes?

DR. HERSHKOWITZ: Let me just comment on the studies a little bit. You know, it's not as though patients receiving vigabatrin didn't come up with UBOs on MRI, but patients not receiving vigabatrin came up with the same. And it couldn't be really differentiated. So the real question to ask is were the studies sensitive enough to pick up a significant difference in MRI. And the studies were not

designed as such. But we can say that there was no statistical difference between the numbers of identified UBOs.

DR. GOLDSTEIN: So is there any evidence that this has any clinical significance in adults? That's the question that was being asked. And the answer is yes, no, or we don't know.

SPEAKER: Yes, no, abstain.

DR. GOLDSTEIN: Yes, no, abstain, but yes, no, or we don't know is what we're really trying to get at. So do we think that yes, there is evidence that this has clinical consequence in adults? Do we think that there's evidence that it doesn't have clinical consequence in adults? Do we not know whether it has clinical consequence in adults?

There you go.

Okay, so the consensus is that the data aren't sufficient to say whether this has clinical consequences or not, or even whether it's a problem or not in adults.

DR. ROGAWSKI: And I'm going to presume -- tell me if I'm wrong -- but I'm going to presume that that answer does not pose a bar to approval.

DR. GOLDSTEIN: That's right.

DR. ROGAWSKI: I mean, I think it should be -- the statement should be there's no evidence supporting a problem in adults.

DR. GOLDSTEIN: That's correct.

Let's -- eight is the second part of that -- is that if the answer was yes to No. 7, should there be additional clinical requirements, additional monitoring, additional analyses? And I guess the correlate to that is that if we don't have the data one way or the other, should there be additional clinical requirements, additional monitoring, or additional analyses before approval? Again -- and this could be part of a risk management scheme also potentially, I guess.

Okay. Comments?

Dr. Weinstein.

DR. WEINSTEIN: That sounds like a research question rather than a clinical question.

DR. GOLDSTEIN: Very good.

DR. CUNNIFF: Can I just clarify something?

DR. GOLDSTEIN: Sure.

DR. CUNNIFF: This issue has --

DR. GOLDSTEIN: You have to say your name for the record. I'm sorry. I've learned my lesson about this.

DR. NGO: Please state your name, please.

DR. CUNNIFF: Tim Cunniff from Ovation. It was a clinical research issue due to the findings of intramyelinic edema. At some point in the '90s, there were seven studies in adults and five studies in pediatrics. They all had pre-specified prospective MRI monitoring, and there was no finding suggestive of IME. So it has been looked at already.

DR. GOLDSTEIN: So should there be

additional clinical requirements related to this?

Dr. Rizzo.

DR. RIZZO: So the anatomical data are important. What about behavioral data? Is there evidence on cognitive decline in relation to this potential intramyelinic edema? Have any studies been done? And this could be a clinical question, because one could administer neuropsychological tests.

DR. GOLDSTEIN: I'll have Dr. Sagar answer. But there's also autopsy data and biopsy data where it was the same. And Steve, you can talk about --

DR. SAGAR: The data is that there is no -- neuropsychological testing has been done in randomized trials of vigabatrin. There's no difference between the vigabatrin-treated subjects and the placebo-treated subjects on neuropsychological performance. And there was no clinical change noted in the very same studies in which the MRIs were performed.

DR. GOLDSTEIN: Very good. Any other comments?

Okay, so let's try this one. Should there be -- make sure -- okay. Should there be additional clinical requirements, additional monitoring, et cetera, related to intramyelinic edema before approval? Yes? No? Okay. So for the record, the consensus was no.

Okay. So now let's turn to the monitoring plan, which again, we've heard a fair amount of discussion about -- which we've had a fair amount of discussion about already. So -- and this gets to under what circumstances should it be approved. And I guess the first part was should there be a risk evaluation and mitigation strategy? And let me take the prerogative and say that that's all we've been talking about. So the answer to that is yes. So I think we can move past that.

Then, should continued access to

the drug be linked to ophthalmologic monitoring? And again, let me just take the prerogative -- that was a good deal of what we were talking about. And even though this may cause some restriction, I think the consensus was that yes, that monitoring should take place as part of this risk strategy.

Another question was in terms of the frequency of the monitoring. And that's what we had the discussion about before. I don't know that we need to discuss this again. The only point that was made earlier was that this needs to be considered in terms of the real world reality, but I think we've dealt with that.

Is the sponsor's plan for monitoring adequate? And again, I think we've talked a lot about this, at least in terms of the frequency and many issues related to how the monitoring should be done. I'm open to further discussion if there is

any.

Dr. Kramer.

DR. KRAMER: I'd just like to clarify something. I think it's important for us to be explicit about why -- actually, some of the decisions have even already made. For instance, why the Committee feels that patients have to be intractable and why we're requiring the REMS. And I think we should be clear about the data.

I heard Dr. Mizrahi quote several times 40 to 60 percent of patients may experience a defect. That's not what I saw when I reviewed the background packet.

I may --

SPEAKER: (inaudible)

DR. KRAMER: Okay. Because I thought I was seeing like 25 to 30 percent.

SPEAKER: (inaudible)

DR. KRAMER: Okay. So I think it's important for us to clarify. Are we stating that our reservation about broader use is because the sponsor hasn't demonstrated

specifically in this refractory population in a very formal way that we have added benefit, or is it because of the sheer frequency of this side effect that may or may not have -- in the balance of effectiveness and risk -- be critically important to individual patients and their decision?

I just think we should be clear here.

So I'm getting a sense -- my sense from listening is that it's because of the frequency of the visual field defect. But I want to be clear, because I think we should be clear about what we're requiring and why.

DR. GOLDSTEIN: I think -- and again, let me try to summarize -- and people can comment. But I think it's actually a combination of the two. I think it's a combination of the questions that there were about -- you know, what drugs were used to establish refractoriness and how that's defined, combined with concerns about the potential

toxicity if the drug was totally safe. I think we'd come down risk/benefit on one way but it's not totally safe.

So I think it's a combination of the two.

DR. KRAMER: The thing that's bothering me is we haven't talked -- these other alterative drugs have serious toxicities.

DR. GOLDSTEIN: Yes. And that's part of the balance.

DR. KRAMER: Very serious toxicity. So you know, why have we made this one -- why are we saying this is intractable, last resort? It seems to me that the discussion is the frequency. When you're dealing with a 25 -- you know a quarter to a third of the patients having something, people get nervous. But I just want to clarify that.

SPEAKER: It's also the irreversibility of this adverse -- serious adverse effect, I think, has to be thrown in with the incidence or prevalence.

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: Yeah -- no, I think it's the totality of information about (inaudible). I think irreversibility is a part of it, although we have other drugs that cause very rare but irreversible, very bad things, too. We don't make them the fifth- or sixth- -- second-line or third or fifth-line drug. I think it is largely the frequency. I think it's largely -- we've heard various estimates but 30, 50 percent, whatever it is -- I think it's largely related to how common it is.

DR. GOLDSTEIN: Dr. Crawford.

DR. CRAWFORD: On a different area of the REMS -- the proposed REMS plan -- when I look at the patient caregiver education, primarily it's the medication guide -- there's a few other aspects under the communication -- I just think that's quite adequate, because from everything we've heard today, there's a middle ground between baseline to give out the initial

warnings and absolute dis-continuation of the drug because of obvious visual defects. But we know there can be some vision changes that are not definitive yet. So I do think if there are any vision changes, realizing some of it could be (inaudible), but I simply think the specified REMS should state the need for enhance risk communication to patients -- reminders much more specified about if there are any visual disturbances to let them know. Again, something might be happening. We're not quite sure. It needs to be specified more.

In terms of a black box warning, I certainly think there should be one. I'm not sure as to either it only needs to look at PVFDs and MRI warnings. I just don't know, so it's not necessarily a suggestion, but definitely in the labeling, be it in a black box or elsewhere, I think there needs to be some language as to the fact there's insufficient evidence to determine whether there's a causal relationship in the

development of central vision loss.

And FDA staff -- of course senior staff, can correct me if I'm wrong, but I think precedent was kind of established with that with saying we just don't know if it kind of causes these problems, but it's strong enough to give it a high warning.

DR. GOLDSTEIN: Other comments?

Dr. Sleath.

DR. LESAR: Yeah, just some mechanics related to the REMS. There needs to be much more specificity in terms of the visual field evaluation and its tracking. That is, if there's discontinuity in practitioners, who is watching how things progress or don't progress? And will that be done by the company? And also a question that relates most to this -- to five and if you go back to Question No. 4, which is what happens -- and Dr. Crawford's point -- well, what happens if there's detected visual field loss?

Let's say it's even found to be

moderate to severe. Will the decision be the companies to not provide the drug and require a taper, or will it be up to the patient and the prescriber?

DR. GOLDSTEIN: Dr. Sleath?

DR. SLEATH: I just had a clarifying question. It said that the first initial prescription had to be written by a board-certified neurologist, and I agree with that. But then what about that second prescription, when you're deciding whether to go in maintenance phase? To me, it should be the first and second, and then if you have to move to non-neurologist for accessibility, I'd like the neurologists kind of to comment on that. But to me, it makes me nervous to just say the first one is the board-certified neurologist and then they could switch.

DR. GOLDSTEIN: Dr. van Belle, and we will get to that.

SPEAKER: (inaudible)

DR. GOLDSTEIN: Yeah, why don't we do

that. Maybe one of the epileptologists can respond to that. My own thing is that we do this all the time. We prescribe a drug, we follow a patient, and then or a drug to be renewed, very often the specialist will do the renewal instead of the primary care physician. There can be a whole variety of mechanisms and ways of doing that.

Any other comments from any of the epileptologists here about that?

DR. JENSEN: Frances Jensen. I just wanted to mention I heard the word potentially -- you know, mandated dis-continuation of a drug -- if some milestone was met in terms of an adverse effect. And I think this has wound up with who is monitoring the patient. I don't think -- I think there are many -- we heard from the audience, and I think it's shared among many of the epileptologists, that it's very individualized. There might be patients who are willing to tolerate a significant visual field deficit for a variety

of reasons because it may not impact their life to the extent that these seizures do. So making an arbitrary -- you know, cutoff of drug supply to a patient, I think, would not be a good thing.

In addition, I think if a re-evaluation by a neurologist or an epileptologist should be triggered by a change in some of these follow-up procedures such as the visual fields, because you would not want the primary care physician perhaps to be the only person helping the patient decide to come off the medication when it might require a more balanced decision-making process by somebody who has greater expertise, who can have a more extensive discussion with the patient to determine whether for that patient it would be the right time to come off or not.

DR. ROGAWSKI: I, too, was very troubled by this automatic cutoff provision that the sponsor provided in their risk management

proposal. For all anti-convulsant drugs, going cold turkey can be really problematic and can induce seizures and sometimes status epilepticus. For this type of antiepileptic drug, and for vigabatrin in particular, it's particularly problematic, because there is some suggestion that dis-continuation of the medication is associated with rebound seizures.

So this could be problematic.

DR. CUNNIFF: If I could just address some of the questions -- I'm sorry, Tim Cunniff from regulatory at Ovation.

To address some of the questions, what we want to do with the mandatory ophthalmologic monitoring, we want to ensure that the patient on the appropriate time frames is seeing the ophthalmologist within their ophthalmologist. So when we mandate that that visit has to occur, we're ensuring that that relationship exists.

And if the patient does not see the ophthalmologist or the neuro-ophthalmologist

and we give some flexibility there, that's when we would make a decision that if you're not going to follow up with the testing paradigm, you probably should not be on this drug. And then there would be a taper down. Obviously, we can't cut people off. We have to taper down about a half a gram every three or four days. And so you would dispense enough for a taper in that case.

But we're trying to leave the practice of medicine to the epileptologists and to the neuro-ophthalmologists. If there is visual field loss, we don't mandate that they come off a drug. Either that's a benefit/risk decision between the patient, the caregiver, the neuro-ophthalmologist, and the epileptologist. And that, we think, is appropriate.

DR. GOLDSTEIN: Dr. van Belle.

DR. van BELLE: I need to be calibrated. Is there a program like this for felbamate?

DR. GOLDSTEIN: FDA? He's asked whether there's a program for felbamate.

DR. KATZ: No. You mean a REMS or REMS-equivalent? I don't believe so. I think there's a consent form. Not a consent form, but a form that patients sign that says I've read this information; I know all about this. There isn't -- there actually was originally a requirement, so-called in labeling, to draw CBCs very frequently. And we actually removed that requirement a number of years ago because there were massive numbers of negative lab tests. And it wasn't worth it from a cost benefit.

There is no equivalent program like this. There is a program like this for other drugs, but not for felbamate.

DR. van BELLE: So my question is whether it would be adequate to have the restrictions in terms of prescribing it. We talked about before the lack of advertising. Is that enough or do we really need this program?

DR. GOLDSTEIN: Well, again, if there

is an analogous program -- you know about clozapine. You can't get your next prescription filled unless you have blood drawn.

And with Tysabri, there is a requirement that -- patients, before they get their infusion have to have a checklist administered to see if they've had any symptoms since the last infusion referable to possible case of PML. And basically, those checklists have to be filled out and sent back to the sponsor, and at least periodically. They don't get their next treatment if they haven't sent back the checklist. So there are relatively analogous programs for other drugs where there is basically a requirement imposed that certain testing be done.

Dr. Nelson.

DR. NELSON: I think it's been alluded to and it's probably part of the plan, but I think this post-marketing surveillance concept has to be strictly enforced. I know that there

is going to be annual submission of data to the FDA. It's not clear totally to me what that's going to contain. And, for example, are they going to be looking for intramyelinic edema and these other problems as they develop? You know, I know they plan on looking for efficacy and kind of some gross general ideas. It just has to be very clear what that's going to contain.

The other question, or the other comment, I think really has to do with medication guides. And I know -- you don't have to wordsmith it right now, but I strongly encourage, when you're sitting down to talk with the company, that FDA really looks at the tenor of the wording. Because just a quick read of it -- I don't know if this is a real one or not, but it says something like one-quarter of adults may lose some peripheral vision. And I think that's actually misstating it, because I think one-quarter of adults will lose some peripheral vision.

And just the wording of that makes it sound like it's much less of a risk than it really is. And nor does it really suggest the irreversibility of this and the progression of this, and the unknown nature of what's going to happen as time goes on. I think it has to be worded in such a way.

You know, patients -- and we all have experienced this, where you say something to a patient and they completely misunderstand what you're saying. And it has to be so clear that we're explaining to them that this is a very dangerous thing that they're undertaking. Although there are benefits; Clearly there is a real risk. And it just has to be super clear.

DR. GOLDSTEIN: Dr. Kramer.

Yes, we had you on the list. We had you on the list next.

DR. KRAMER: Well, I'm just going to stick my neck out here and say it strikes me that the critical intervention is requiring that

the patient interact with a board-certified neurologist and get appropriate evaluation and counseling. And I'm very nervous about even the requirement that if they don't show up for the ophthalmologic testing at a certain time, that they are tapered off of the drug.

Because I can imagine scenarios where there's lots of reasons why patients can't get there for that initial ophthalmologic testing.

And I'm just wondering, is it adequate? Should we be focusing more on being really clear in our risk communication to the doctors and to the patients about what's at stake and what kinds of risks they are willing to take, and that we maybe create a more-explicit patient agreement of what responsibility they're taking for their own decision to be on this drug, and a full understanding of the risk of visual field loss, its frequency, its irreversibility, et cetera, as opposed to feeling that we can

mange the whole thing with all of the attendant restrictions and access that that implies.

So I'm just curious what those of you who take care of these patients think. And I just know that transportation and reality of their lives might make this very difficult.

DR. GOLDSTEIN: Dr. Gorman.

DR. GORMAN: Dr. Kramer hit the high points of my thoughts as well, because I was going to respectfully disagree with Dr. Nelson. And I think the escape language for this REM has to also be very explicitly. To use an anecdote, because of the scheduling of this meeting, I had to cancel my physician's appointment, which is once every six months. And despite being in one of the most physician-rich states in the nation, I cannot repeat my appointment in less than 45 days. So that restriction seems to me to be onerous.

So I think that there needs to be

an escape hatch, and I think -- I agree with Dr. Kramer that we can think we can manage this and we can attempt to detect things early, but that's no -- looking at the sensitivity and the specificity of this test, I wasn't terribly convinced that even with the management programs that we have in the hands of different technicians, that we're going to be able to be 100 percent successful in that particular effort.

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: We have experience with at least one drug, probably more, which suggests to us strongly that no matter how intensive an educational campaign is or a communication plan, if you think there's a test that should be done periodically, if you don't somehow require that that test be done, whether it's you don't get your next prescription until the test has actually been done and the report submitted, whatever it is, I think we have pretty good reason to believe that unless you require it

somehow -- link it to drug access -- it doesn't get done. And education campaigns just don't seem to really make it happen without some sort of drug linkage to the performance of the test.

I think in any system where you would link it to the drug, of course you're going to build flexibility and you're not going to say if it's not 90 days later, you've got to be tapered off. Of course, we would build some flexibility. We understand that there are cases where real life intervenes. But if you think the test should be done, there's really no way to ensure that it gets done unless there is some linkage to access to drug, however flexible.

DR. GOLDSTEIN: Let's see.

Dr. Gardner, Dr. Vega, and then Dr. Rogawski.

DR. GARDNER: I have similar concerns to Dr. Kramer's, and I think in particular, it's not clear to me who is going to be doing this tapering.

The company is going to be doing the tapering? Because if they -- if SHARE recognizes that they haven't had an ophthalmologic exam, then the company is going to taper then off? This doesn't seem reasonable to me.

At the risk of temporizing, because we've been down this road with other drugs before with some problems, I'd like to see how people would feel about taking an interim step, which is all of the requirements for neurologists -- epileptologists' management of their patients and a registry as proposed by the company, and follow that company with the data that you have listed on your slide as to be collected, and ascertain after a reasonable period of time whether people are in fact getting back with adequate communication to physicians and to patients about the importance of getting their exams.

And if we find that they are not getting their exams after some reasonable

period or time or inadequate numbers that it's a problem, then analyze what that problem is and take the next step. But to prescribe here that the company should oversee this and begin to taper patients who don't get in by such and such a date just doesn't seem reasonable to me as a way to go.

DR. GOLDSTEIN: There are a number of logistical ways that I think that the FDA could discuss with the sponsor to do this. For example, contacting -- if the patient misses their ophthalmologic evaluation, contacting their prescribing neurologist. Letting them know that, and tell them that it needs to get done or else their -- you know, the wording could be worked out. But I guess that's what they're trying to get at.

Dr. Vega.

DR. VEGA: This is something that I want the sponsor to clarify for me. Did you discuss your patient materials -- educational materials -- with patients? And what kind of

patients? Because I think it's important to include all socioeconomic status in terms of location, gender, race, ethnicity among some groups.

And this is a story I always tell. Some of the patients -- some of the groups that I work with, the Hispanics, one word can make a big difference. And I will give an example of a woman who came to the emergency room with seizures, not as a result of what we've been talking about today, but as a result of an overdose because on her prescription bottle it says take once a day. But once in Spanish is 11 times. Eleven. So the woman took 11 pills. And for me, it's very important the pilot testing phase of any educational materials. So I want to know how does that.

DR. GOLDSTEIN: And I believe Dr. Sleath had also made a similar comment about testing the patient education materials beforehand.

DR. CUNNIFF: Tim Cunniff from regulatory at Ovation. Some very good questions. With respect to the patient medication guide, we started actually -- there is a patient medication leaflet approved by Health Canada, and so we market the drug in Canada.

In addition to the physicians' label, we have that labeling approved through Health Canada. So we started with that. We have not gotten into labeling negotiations with the FDA yet, so once we do that, then we'll do all the readability and comprehensive testing. We're also very cognizant and we do -- we're a small company, but we have drugs throughout the world. We're very cognizant about what you say about a straight translation.

So we use a translation service that not only does the little translation and they have a clinical person go through it to make sure that the message is preserved as

well. So that's a translating service that we use to make sure our labeling around the world is communicating what it's supposed to be.

DR. VEGA: But I think the people who actually will give you the best evidence if that is really working are the patients. So having a clinical person evaluate the materials is really not necessarily giving you the answer that the patient will understand.

DR. CUNNIFF: That's a good point. I don't know if the FDA wants to comment on the process of the medication guide. Maybe what type of testing is done once we do agree to the language. I'm not sure if you guys have a formal process. We can incorporate, I think, some of the concerns as we do it.

DR. GOLDSTEIN: Again, the purpose of the discussion -- we're not taking a vote on this. This is for the FDA to hear everybody's opinions, and they can then sort through all the things that they've heard. I don't think there

is something specific to vote on for this, but a couple of other -- unless the Committee wants to. A couple of other comments and then I think we'll close this section out.

Dr. Rogawski and then Dr. Jung. You were on my list.

DR. ROGAWSKI: I wanted to raise an issue about another safety concern, but I think we ought to do that after we finish talking about the REMS program. Are we finished with that or are you going to take a vote on it?

DR. GOLDSTEIN: This is all part of it. Yes. I'm sorry, she was asking me a question while you were talking. I didn't get your whole question.

DR. ROGAWSKI: Oh, I'm sorry. My question was, I wanted to raise another entirely separate safety issue that hasn't been raised before during today's deliberations.

DR. GOLDSTEIN: I think that's fine. Go ahead.

DR. ROGAWSKI: Okay. Well, Dr. Katz

in his opening remarks indicated that the Committee is free to raise issues that the Agency hadn't previously raised in their questions. And the issue that I'd like to raise is the concern -- the potential concern that vigabatrin may in some patients exacerbate seizures and indeed cause status epilepticus. This concern was brought to my attention in reviewing the documentation and in looking into the literature on the intramyelinic edema issue.

The rat study that is relevant there is the Gibson 1990 paper. If you look at that paper, rats were treated with clinically significant doses of vigabatrin. And a high proportion of those rats had seizures -- continuous seizures -- in fact, throughout the entire period of administration.

And contrary to what the sponsor notes in their dossier, the seizures didn't stop after three months in the rats, but rather, they stopped three months after the

drug was discontinued. So they continued for a period of time after the drug had been discontinued.

If you look at the integrated -- if you look at the integrated database that reflects additional histological studies that were done later on, you'll see that a significant portion of those animals also had seizures. So then I went back and looked at the clinical data. And in the pivotal trials, I noticed that three out of the 222 patients who had been taking vigabatrin in the two pivotal trials had status epilepticus where zero had status epilepticus in the placebo group.

And three of the vigabatrin-treated patients were described as having convulsions, whereas zero of those 135 placebo patients were described as having convulsions as a reason for discontinuing the medication. Now, of course, these were epilepsy patients. They were having seizures

and so it's a little bit hard to interpret that.

But then if you look at some of the other reports in the literature, you'll see that this pattern keeps repeating itself. So in this Chadwick study that I described earlier, which was this head-to-head comparison between carbamazepine and vigabatrin, a total of seven out of 229 patients treated with vigabatrin had exacerbation of seizures, whereas zero out of 230 with carbamazepine had exacerbation of their seizures. There's a Polish study that was published in 2005, an open-label trial, where they reported that two out of 26 patients had increased numbers of seizures.

So I think there's substantial evidence that vigabatrin in animals certainly causes seizures. That's very clear in rats. And perhaps suggestive evidence in the clinical population as well. And I gather that this isn't terribly surprising. The

only other anti-convulsant drug that has anywhere near a similar mechanism, tiagabine is known now to exacerbate seizures. And gabapentin, of course, also has this concern, as well.

So this is an area that hadn't been raised in any of the discussions -- any of the documentation -- regarding how the proposed labeling was going to come together on this. And so I felt that this was an area that needed further investigation.

DR. GOLDSTEIN: Thank you.

Sponsor?

DR. SILBER: Chris Silber, Ovation. We certainly recognize the risk of status epilepticus, particularly in a refractory complex partial seizure population. What we've included in our proposed labeling as a summary statement and warning with respect to status epilepticus is that in Phase III studies, 2.3 percent of vigabatrin-treated patients, as compared with 2.2 percent of patients treated

with placebo, were noted to have status in those controlled studies.

SPEAKER: (inaudible)

DR. SILBER: I'll have to go back over the data and look at that.

DR. GOLDSTEIN: Okay, Dr. Jung.

DR. JUNG: A couple of points. Dr. Gorman mentioned that he had to reschedule a physician's appointment and it took him 45 days to get back in.

And one of my concerns is that the patient population we're talking about is frequently a lower economic class -- patient population who may not have the insurance coverage that Dr. Gorman might have. And that population, unfortunately, has even poorer access to specialists. The other point I'd like to make is that with this meeting I suspect we probably took the access of the neuro-ophthalmologists in this company down by about 75 percent, which means that a patient who is waiting for his or her three

month neuro-ophthalmologic evaluation is now pushed back six or nine months. And that's assuming they have good insurance.

The TOUCH program with Tysabri has allowed for a very structured follow-up process. And it may not be reasonable, perhaps, for the FDA and the sponsor to get into this. I guess this is something for you to negotiate, but the TOUCH program -- one of its strengths has been that it really does allow for very close follow-up of patients.

And so I would urge that we use a model similar to that, whether it's with a registry to make sure that patients don't fall through the loops.

You know, we talk about physician monitoring of patients, and even with the best of intentions communication between physicians offices, between the neuro-ophthalmologists office and the epileptologists office may not always occur in a timely manner. And again, there's a

risk that our patients can fall through the cracks as a result.

The other point was that on the other hand physician and patient complacency is a real big danger, even when people have been warned about the dangers of a drug. And I've frequently been frightened by patients who have come back in to see me after they've had their drugs renewed by their primary care doctor in the distant neverlands of Eastern Washington or Idaho or Montana. I hope there's nobody out here who is going to be offended.

You know, patients want it because of convenience. Primary care doctors out in the hinterlands do it because of patient interest of service. But sometimes there isn't the recognition that we could be missing something dangerous because the specialist is not following up. And so I don't mean to -- you know, negate the value of our primary care docs out in the

community, but I think it's really important that the specialists do -- who are responsible for these patients -- do hang on to these folks. So that's my push.

DR. GOLDSTEIN: Okay. One last comment from Dr. van Belle and then Dr. West.

DR. van BELLE: Getting back to the point of exacerbation. It's always struck me that looking at only patients that have a 50 percent decrease in seizures is a little too optimistic. And what we should really do is also look at the patient that has a greater than 50 percent increase in seizures. And it wouldn't be very hard to get that data just to look at it and to see whether in fact this is going on as well. And I think that's a fairly straightforward thing that the sponsor could do.

DR. GOLDSTEIN: I guess that would be part of this follow-up registry as well.

Dr. West, I think you had your hand up. I didn't see it. Sorry.

DR. WEST: I did. And I wanted to

elaborate on Dr. Jung's question.

So Dr. Rogawski is following this patient with complex partial seizures. They're started on vigabatrin. They come to me for their first visual field test and then it's two or four months later they no-show. I call them. Gosh, their phone is disconnected and their other contact number, they pretend they don't even know, or maybe I leave a message and they can't get them.

So I call Dr. Rogawski. He does the same thing, and now we're in a situation where nobody can get a hold of this family. Now what happens? I mean, this happens all the time.

DR. GOLDSTEIN: Right. And unfortunately, patients then run out of medications if they have no contact with the physician.

DR. WEST: So a structure in place I think is important. A backup plan.

DR. GOLDSTEIN: Okay. For the FDA

standpoint -- you know, we've had about a good 45 minutes, hour discussion of various points related to this risk management plan. Is that sufficient for your purpose? Good.

Okay, well, the final thing that we need to vote on, and I was told that we could go over a little bit since this is a two-day meeting -- so that's why I let us talk a little bit more -- was that we have to vote on the final question, which is No. 9.

Given the data in hand, does the Committee recommend that Sabril be approved for treatment of complex partial seizures in adults? Having said that, that's with all the provisos, all the other things that we've talked about. Given the data in hand, does the Committee recommend that Sabril be approved for the treatment of complex partial seizures in adults?

Before we do the actual vote, time for comment.

Dr. Crawford.

DR. CRAWFORD: A question. Does this mean that the Committee would not be recommending approval in a less than pediatric populations?

DR. GOLDSTEIN: This is in adults. That's all we're dealing with today, is in adults.

DR. CRAWFORD: What age does adult start?

DR. GOLDSTEIN: Well, with my son? When he's 50.

Who's next? Dr. West. I'm sorry, Dr. Katz wanted to clarify something.

DR. KATZ: Yeah, I think it usually means and above, or above 16.

SPEAKER: Asthma, they count it over 12.

DR. WEST: I'm not sure if this is a typo, but I feel like things are being changed here. It says be approved for the treatment of complex partial seizures in adults. I thought we were talking about refractory complex partial

seizures.

DR. GOLDSTEIN: Yes.

DR. WEST: I just want to make that clear.

DR. GOLDSTEIN: That was with all of the provisos and all of the issues that we talked about earlier. That's exactly correct. It's refractory, and we defined refractory as failing -- refractory to several other anti-convulsants.

DR. WEST: Refractory is left out of this.

DR. GOLDSTEIN: Yes. Could we -- we can't type it in here, unfortunately, but that's absolutely correct.

DR. WEST: Thank you.

DR. GOLDSTEIN: Other comments.

Dr. Jensen.

DR. JENSEN: Just one procedural thing. So we make a vote and this is just an advisory Committee. And you ultimately will take all of this information. This is just an

advisory vote.

DR. KATZ: I'll tell you what it's going to say in the newspapers tomorrow.

SPEAKER: The Committee is advisory, but the FDA usually follows their advice.

DR. GOLDSTEIN: That's right. But not always.

DR. KATZ: Not always. It doesn't usually say that in the papers. We reserve the right.

DR. GOLDSTEIN: The Secretary reserves the right. Dr. Mizrahi.

DR. MIZRAHI: Could we -- Dr. Katz, could you talk a little bit about the lower age range of this recommendation, and whether 16 is as low as we could go within the confines of what is being asked here?

DR. KATZ: I say about 16, because from a regulatory point of view, pediatrics is defined, I think, as 16 and below. So we define adults as above 16. However, having said that, it's not uncommon for antiepilepsy drug programs

to include in their trials patients down to the age of 12. So we can go back and look at what the lower age limit was actually in the trials. I don't recall off the top of my head what the lower age limit was. We tend to --

DR. MIZRAHI: Because one of my concerns will be that we'll be here for two days, and then actually there will be a gap in terms of our age -- of what we're addressing in terms of age with coming down the lower limit for adults and then focusing on the infantile spasms population, which could be the sub one year range. And the population that we're really in many ways most concerned with and what we heard a lot about today would not be addressed.

DR. KATZ: That's very likely to be true, assuming that you recommend or that we approve the drug for infantile spasms. I don't mean to pre-suppose anything but just for argument sake, it's not uncommon. Typically when anti-convulsants are approved, they're

initially approved in adults. Or if they study down to 12, down to 12. And then there's no evidence in any population below that age.

There is a requirement in the law that if a drug is developed -- approved in adults and the disease exists in pediatric populations, that sponsors have to ultimately do studies in those younger age groups unless for some reason we decide they shouldn't.

So ultimately, there would be a requirement to do that unless we decided it's too dangerous to study -- you know, to study it in 6-year-olds with complex partial seizures. So that's a determination to be made in the future.

DR. GOLDSTEIN: Dr. Weinstein.

DR. WEINSTEIN: Just a question for clarification. Earlier, it was said no advertising.

Could somebody define what "no advertising" means? Is that advertising in this country? They can load the journals

coming in from elsewhere? What does no advertising mean?

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: Well, again, I'll just reiterate what Dr. Temple said, which is we don't have the authority to say that a company can't advertise. There are rules about what you can say in advertising, but if we approve a drug for marketing, I'm not aware of any rule that allows us to say but you can't advertise for it.

DR. GOLDSTEIN: The United States and New Zealand.

Dr. Vega.

DR. VEGA: I'm just curious about something. We got a lot of testimonies from the public for the children component, but very few -- only today we got one for adults from the public. Does anybody have any idea why that happened in terms of the public testimonies?

DR. GOLDSTEIN: Dr. Katz.

DR. KATZ: Why what happened? Why it was used in children?

DR. VEGA: No, no, no, no, no. A lot of the public testimonies that we got online before today of people trying to encourage us to approve this medication was for parents who want this approved for children and grandparents. But we really didn't get much about adults.

DR. NGO: Rusty, I can answer that. In the FR Notice, I'm the one who everyone sends their testimonies to, and it's open to the public and all the testimonies I got were in the FedEx package before and in your package today, and that's all I got. So I can't answer to why adults with CPS didn't write in, but apparently it's mostly parents of children with IS.

DR. GOLDSTEIN: Very good.

Yes, Dr. Kramer.

DR. KRAMER: Could the sponsor just clarify whether the patients went down to age 12 in the pivotal studies?

DR. CUNNIFF: There were five trials being undertaken in patients with pediatric complex partial seizures. Due to the finding of

intramyelinic edema, those trials were suspended early.

DR. KRAMER: In the two pivotal trials what was the age range?

DR. CUNNIFF: Oh, the two pivotal ones?

Dr. Silber?

DR. SILBER: In the two pivotal trials, age 18 was the lowest age.

DR. GOLDSTEIN: Dr. Crawford. More comment?

DR. CRAWFORD: A quick question, again, for the sponsor. If the FDA were ultimately to approve this product for CPS in adult patients, does that mean any child below whatever age is the cutoff would not be enrolled in the REMS program and would not have access to the product at all?

DR. CUNNIFF: I think to address that, what we don't want to do is regulate the practice of medicine. So if the label is 18 and above and the patient was 17-1/2 and the

neurologist decided to treat them, we would not interfere with that. What we do want to do is in all the physician attestations, we're very clear as to what exactly the indication is. And the neurologist would have to attest that he understands the approved indications which encompass the patient population and all the safety and the monitoring provisions of that.

And again, when we collect -- we are going to collect all the data via a registry, and we'll sit down -- we're going to have a steering committee of ophthalmologists and neurologists. And we have to make the reports to FDA. And I think if we saw significant use in patient populations where there would not be approval we would have to adjust the REMS to make that a more rare exception.

DR. GOLDSTEIN: Dr. Dure.

DR. DURE: Does this mean that because you have multiple attestations from patients, that you'll get that from minor children?

DR. CUNNIFF: With respect to pediatric complex partial seizures?

DR. DURE: Yes.

DR. CUNNIFF: We have submitted a plan to FDA to restart that program. Again, it's required by law to look at it. And we've made some determinations as to what appropriate age limits would be appropriate. I think the FDA position is they wanted to see what happens with the adult indication before we consider the pediatric CPS indication, but we're willing to pursue that program.

DR. DURE: No, but my question is that you said that if you had somebody who was 17, which also means probably if you had a 16-year-old who was enrolled in the program, that you are obtaining multiple attestations from people according to your REMS. So you would be doing that with minor children. Is that correct?

DR. CUNNIFF: Correct. Yes. And it's written that way, too, the attestations because

maybe the cognitive ability of the adult. They may be older but they may have the cognitive ability. So that's all in there as well.

DR. GOLDSTEIN: Dr. Kramer.

DR. KRAMER: I think you just answered -- I just want to make sure that off-label use will still be captured in the registry. Okay.

DR. GOLDSTEIN: Dr. Jensen.

DR. JENSEN: I just want to clarify. So this would -- if it's approved in this way for adults, does this mean that it could not be given under any circumstances to people under, say, 16 on an off-label fashion at this point in time? Is that what you're saying? Or not? Be explicit.

DR. KATZ: From our point of view it would be very unusual. There are other cases where physicians have to attest that I've read this, I know what this is indicated for, I know what the risks are. In those cases, not that we have very many, but in those cases I think it's

pretty unusual to require the physician to say and my patient has the thing that it's indicated for. In other words, usually even those restricted conditions permit off-label use as long as the physician understands what it's approved for.

DR. JENSEN: It wouldn't be part of the SHARE thing, right? I mean, say you --

DR. KATZ: No. And we're not, I don't believe, contemplating, for example, contraindicating it in people below 18, which would really be how you would operationally prevent off-label use. So I think probably the company anticipates that there could be off-label use. But those people will be -- and it could be adults who have a different seizure type, I suppose. But everybody would be included in the registry and be subject to the same restrictions that the on-label population would be.

DR. GOLDSTEIN: Dr. Rogawski.

DR. ROGAWSKI: Yes. Just to clarify

this issue of off-label use. There have been reports in the literature suggesting that vigabatrin is good for a variety of other indications beyond epilepsy, including drug abuse and so forth. How do you perceive the risk management program that the sponsor is describing as being able to interdict that type of activity that might be problematic?

DR. KATZ: Well, I don't think we've thought in great detail about how to do that, but of course, it's an issue. And there are things you can say in the documents -- there's no evidence that it works in anything other than this. There's no evidence that it's safe in any other population even with this monitoring. So there are things you can build in. But unless you say something like -- unless, as I say, you require the physician to attest to the fact that their patient has the labeled indication, or you contraindicate it in labeling that anybody who doesn't have complex -- any non-adult who doesn't have complex partial seizures -- unless

you do something like that, I don't think you can prevent it entirely. But you try to make it clear to people that this is the only thing we have information on and it has a bad side effect.

DR. GOLDSTEIN: Let's, I think -- I think we've had a thorough discussion. Let's go ahead and address the question, which by the way, PowerPoint, refractory has been added into the actual statement.

Given the data in hand, does the Committee recommend that Sabril be approved for the treatment of refractory complex partial seizures in adults, again, with all of the provisos and all of the things that we discussed? This we do need to vote on, so press your buttons.

How are we doing? Okay. So for the record, let's start on that side this time.

So first is Dr. Hirtz.

DR. HIRTZ: Yes.

DR. GOLDSTEIN: Dr. Mizrahi.
DR. MIZRAHI: Yes.
DR. GOLDSTEIN: Dr. Weinstein.
DR. WEINSTEIN: Yes.
DR. GOLDSTEIN: Dr. Jensen.
DR. JENSEN: Yes.
DR. GOLDSTEIN: Dr. Chugani.
DR. CHUGANI: Yes.
DR. GOLDSTEIN: Dr. Dure.
DR. DURE: Yes.
DR. GOLDSTEIN: Dr. Snodgrass.
DR. SNODGRASS: Yes.
DR. GOLDSTEIN: Dr. Gorman.
DR. GORMAN: Yes.
DR. GOLDSTEIN: Dr. Heckert.
DR. HECKERT: Yes.
DR. GOLDSTEIN: Dr. West.
DR. WEST: Yes.
DR. GOLDSTEIN: Dr. Rogawski.
DR. ROGAWSKI: Yes.
DR. GOLDSTEIN: Dr. Vega.
DR. VEGA: Yes.

DR. GOLDSTEIN: Dr. Sleath.
DR. SLEATH: Yes.
DR. GOLDSTEIN: Chair, yes. Dr. Jung.
DR. JUNG: Yes.
DR. GOLDSTEIN: Dr. Rizzo.
DR. RIZZO: Yes.
DR. GOLDSTEIN: Dr. Balish.
DR. BALISH: Yes.
DR. GOLDSTEIN: Dr. Lu.
DR. LU: Yes.
DR. GOLDSTEIN: Dr. van Belle.
DR. van BELLE: Yes.
DR. GOLDSTEIN: Dr. Crawford.
DR. CRAWFORD: Yes.
DR. GOLDSTEIN: Dr. Kramer.
DR. KRAMER: Yes.
DR. GOLDSTEIN: Dr. Gardner.
DR. GARDNER: Yes.
DR. GOLDSTEIN: Dr. Lesar.
DR. LESAR: Yes.
DR. GOLDSTEIN: Dr. Nelson.
DR. NELSON: Yes.

DR. GOLDSTEIN: Did I get everybody? Outstanding. Okay, 24 yes, no nos.

Before we conclude, I always like to give the Committee a chance just to make any additional comments relative to the application that they would want the FDA to know about. Things that we didn't quite hit, that weren't covered in the questions.

Dr. Snodgrass.

DR. SNODGRASS: Just the general issue of post-marketing surveillance and what that would actually contain. I think a registry is one part of that, but consideration is given to what kinds of studies could be done to look at specific issues. I'm thinking about, for example, how can you get at the issue of who is going to be a responder and not be a responder. And of those who did develop visual dysfunction, what were any kind of markers that possibly in retrospect might be identified or studies to try to attempt to identify those kinds of issues. Including genetic studies as a possibility.

DR. GOLDSTEIN: Dr. Rogawski.

DR. ROGAWSKI: I just want to reinforce that last comment. I think it's important for the Agency to require post-marketing studies, both for defining the patient population, as well as to get a handle around the toxicity issues. And I would also encourage the Agency to think very hard about the labeling of this product. This is kind of breaking new ground, I think, for any epileptic drugs. So to view this as just another antiepileptic drug that's coming down the pipe I think would be a big mistake here.

DR. GOLDSTEIN: Thank you. Other comments? Very good. So just to remind the Committee, tomorrow we will start at 7:30, Part B of the discussion. Let me also remind the Committee, no discussions off the record about anything related to the matters before the Committee.

Thank the Committee. Thank the sponsor. Thank the FDA. Have a good night.

(Whereupon, at approximately 5:48 p.m., the MEETING was continued.)

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